


Society of Hospital Medicine

SICKLE CELL DISEASE IMPLEMENTATION GUIDE




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Introduction.

Sickle cell disease (SCD) is an autosomal recessive genetic disorder that results from a single amino acid mutation. This mutation in the beta globin gene leads to the substitution of valine for glutamic acid at the sixth position of the beta globin chain, causing the formation of abnormal hemoglobin S (HbS) instead of normal adult hemoglobin A (HbA). In a deoxygenated environment, intracellular polymerization of HbS leads to red blood cell rigidity and a crescent or "sickle" shape to the red blood cell (RBC).[1]

SCD is a multisystem disease that can affect the brain, lungs, kidneys, cardiovascular system, liver, spleen, and bones.

Physiologically, SCD is characterized by recurrent episodes of vaso-occlusion, ischemia with re-perfusion injury, tissue infarction, and hemolytic anemia. The term SCD actually refers to a group of disorders with different genotypes leading to abnormal hemoglobin. Sickle cell anemia is the most common, and severe, form of SCD and includes individuals homozygous for the βS allele (HbSS) or the heterozygous HbS βo-thalassemia. Other genotypes causing SCD are HbSC, HbSβ+-thalassemia, and HbSOArab.

High levels of fetal hemoglobin and the coinheritance of alpha-thalassemia are associated with decreased complications from SCD. As fetal hemoglobin drops by around 5-6 months of age, signs and symptoms of SCD can start to occur and may lead to acute and chronic complications with progressive organ damage.[2–4]

SCD is one of the most common inherited life-threatening disorders in the world. The gene mutation is prevalent in Africa, the Caribbean, the Mediterranean basin, Saudi Arabia, and parts of India. SCD in developed countries is largely due to migration of individuals from these areas of high prevalence. Based on 2008 U.S. Census Bureau information, best population estimates put the number of individuals affected with SCD in the United States between 72,000-98,000.[3–5] However, there are no national registries to accurately understand the true number and impact of the disease.[5] Most U.S. residents with SCD are from racial minorities. Nearly 90% of these individuals are of African ancestry or identify as black, and the majority of the remainder are or identify as Hispanic.[6] The Centers for Disease Control and Prevention (CDC) estimates that SCD occurs in 1 out of every 365 black or African-American births and 1 out of every 16,300 Hispanic-American births.[7] A significant proportion of individuals with SCD are of low socioeconomic status.[8] In a large emergency department (ED) study, over half of patients with SCD were on Medicaid.[9] The cost of managing SCD imposes a large economic burden to patients and their families, many of whom are already financially disadvantaged.[10]

In addition to economic challenges, people with SCD experience stigma and discrimination for a multitude of reasons including race, socioeconomic status, disease status, and acute and chronic pain requiring opioids.[11] Patients perceive discriminatory treatment from the general public as well as from healthcare providers and systems.[12] In healthcare settings, patients with SCD report discriminatory treatment related to their need for opioid analgesics, and often feel they are perceived by providers as "drug seeking". Most patients with SCD are from racial and ethnic minorities and experience racism in healthcare settings. Patients with SCD who report stigma are more likely to have decreased psychological well-being, as evidence by higher rates of anxiety, depression, suicidial ideation, and suicide attempts. They are also more likely to be non-adherent to medical recommendations, have lower levels of trust in healthcare providers, and have higher emergency department utilization.[11,13]

In a study of mortality rates in the SCD population between 1979-2005, mean age at death increased by 0.36 years for each year of the study. The leading cause of mortality in patients under 20 was infection followed by irreversible organ damage and hypersplenism. In patients over the age of 20, irreversible organ damage was the leading cause of death.[15]

The morbidity associated with SCD, particularly vaso-occlusive crisis (VOC), contributes significantly to high healthcare utilization, especially ED and hospital usage. A population-based study of over 21,000 patients from 2005-2006 examined ED visits and inpatient stays. Patients had an average of 1.08 ED visits and 1.52 inpatient stays per year. 20% of the patients had 3 or more combined ED and/or inpatient stays per year.[16] Increased use of the ED by patients with SCD starts in late adolescence, and patients aged 18-30 are the highest utilizers.[17] The hospitalization rate associated with a principle diagnosis of SCD, on a nationally representative sample of hospitals in 2012, was 137 per 100,000 in the U.S. black population, and the average length of stay was 6.23 days.[18]

Readmission rates are substantially higher for patients with SCD when compared to those of the general population.[16] A single center study at a large academic medical center found that 82% of patients with SCD discharged from the ED returned to the ED within 30 days. These patients were hospitalized within 30 days of initial ED visit 58% of the time.[19] In 2010, SCD had the highest 30-day readmission rate of any acute or chronic condition.[20] 30- and 14-day readmission rates were 33.4% and 22.1% respectively, and were again highest in the 18-30 age group.

The Healthcare Cost and Utilization Project from the Agency for Healthcare Research and Quality (AHRQ) recently released characteristics of inpatient stays for patients with SCD as compared with those without SCD. In 2016, there were 134,000 SCD related hospitalizations.[20] Inpatient stays for patients with SCD were far more likely to begin in the ED than for other diagnoses (80% compared to 51%). Discharges against medical advice were more common in patients with SCD than non-SCD patients (4.1% compared to 1.2%). The aggregate cost of inpatient stays for SCD was estimated at $811 million. The indirect cost associated with SCD is difficult to quantify, but most patients report inability to maintain employment or significant loss of time from work.

Increased disease-related complications and ED utilization lead to fragmentation of care after the transition from pediatric care. Adults with this chronic disease often have poor access to primary care. Adult care for patients with SCD is often characterized as non-existent, inaccessible, fragmented or delivered by providers with limited knowledge or interest. This is driven largely by social determinants of health that disproportionately affect patients with SCD. A pediatric hematology practice surveyed their patients with SCD over a sixteen-month period and found that 66% had at least one unmet social need. The examples of unmet social needs included affordable childcare, employment, access to food, ability to pay utilities, and educational attainment.[21]

Given these challenges, many studies have focused on delivery of care to patients with SCD and what the systems and teams should look like for this care delivery. Multidisciplinary teams play an important role in improving care and obviating the need for high utilization. Such teams may work with patients and their families to create individualized care plans, which have shown great promise in facilitating care of patients with SCD. The makeup of these teams varies across hospitals, key roles include inpatient and outpatient internists, family medicine physicians, emergency medicine physicians, nurses, psychologists, psychiatrists, social workers, and case managers. Including social workers and case managers on these teams is especially important in addressing the multitude of unmet psychosocial needs that many patients with SCD face.

For patients who do not have access to comprehensive, specialized care for SCD, telemedicine has been suggested as a method for providing such multidisciplinary care outside of large medical centers.[22] Lack of payment models and technical infrastructure has historically been a limiting factor but may become increasingly feasible as the demand for these services in all aspects of healthcare grows. The COVID-19 pandemic has created a platform for advancing different models to deliver care including more reliance on telemedicine.

The standard of care in SCD is difficult to define. There are very few systematic guidelines based on high quality primary literature. This makes for a difficult situation for health care systems to deliver high-quality care or implement systems of care. The National Heart Lung and Blood Institute (NHLBI) convened an expert panel and published their recommendations in 2014. Various emergency medicine groups have published recommendations for SCD management in the ED. However, in our experience, hospitalists face a variety of clinical challenges in providing high-quality inpatient care for patients with SCD and in safely transitioning patients to the outpatient setting. Many hospitalists have received mixed messages on how to treat pain in SCD. Additionally, hospitalists may not have extensive experience working with hematologists to co-manage patients with SCD. Physicians may lack familiarity with various disease complications and may be uncomfortable managing chronic SCD medications in the inpatient setting. Furthermore, they may not feel confident in determining when patients are stable for discharge and are unaware of discharge-related best practices that can reduce readmissions and improve outcomes for this patient population. This implementation guide has been developed for hospitalists and inter-disciplinary teams to improve care of inpatients with SCD as well as develop quality improvement initiatives to improve outcomes for this patient population. This implementation guide will provide a resource for hospitalists and interdisciplinary teams to provide high quality care to inpatients with SCD as well as develop quality improvement programs to continually evolve this care.

Key Points:

- SCD is an autosomal recessive genetic disorder caused by a single amino acid substitution mutation.
- HbS undergoes intracellular polymerization in a deoxygenated environment leading to RBC rigidity and sickling.
- Physiological hallmarks such as vaso-occlusion, tissue ischemia and infarction, re-perfusion injury, and hemolytic anemia lead to a wide array of disease manifestations.
- SCD is one of the most common inherited life-threatening disorders in the world. In the U.S., 90% of individuals with SCD are of African American ancestry or identify as Black.
- Compared to the general population, patients with SCD experience higher morbidity, mortality, and are of lower socioeconomic status.
- Frequent hospitalizations and rehospitalizations pose significant risk for patients with SCD and the healthcare system at large.

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CHAPTER ONE

Pathophysiology of SCD

There are multiple mechanisms involved in the pathophysiology of SCD. The initial mechanism involves the abnormal β allele in the RBC (HbS or HbS in combination with other abnormal alleles). When exposed to a deoxygenated environment, the abnormal β alleles causes the Hb to polymerize and aggregate. This process causes RBCs to become rigid, fragile, and crescent or sickle shaped. Unlike normal RBCs, which survive on average 120 days, sickled RBCs have a half-life of only 10-20 days.

This episodic RBC "sickling" leads to recurrent vaso-occlusive events with microvascular tissue ischemia and necrosis. The sickling process also disrupts the RBC membrane and can cause hemolysis. Hemolysis leads to the release of free-Hb polymers and arginase into the circulation, which interferes with and lowers circulating levels of nitric oxide (NO). NO plays an important role in vasodilation, and this depletion of NO leads to vasoconstriction, platelet aggregation, and thus the continuation and amplification of the aforementioned vaso-occlusive process. Hemolysis also leads to the release of ferric heme which causes endothelial wall dysfunction and pro-inflammatory effects, further potentiating vaso-occlusion.[2,3,10]

Patients with SCD are at increased risk of severe SARS-CoV-2 (COVID-19) infection, with higher rates of hospitalization, morbidity, and mortality as a result of the virus. This is consistent with studies looking at influenza severity and hospitalization rates in this patient population. A recent study using the SECURE-SCD registry examined COVID-19 cases and deaths in U.S. patients with SCD between March-May 2020. They found a 69% hospitalization rate, 11% ICU admission rate, and 7% mortality rate. The mean age of patients was 29 years. This represents significantly greater morbidity and mortality compared to the general population that contracts COVID-19. Patients with SCD often deal with chronic complications, and the long lasting effects of post-COVID syndrome will need to be further studied. In addition, Minniti et al. recently found a higher mortality in adults with SCD and COVID-19 especially if the patients were older than 50 yrs old.

Acute Pain Crisis/Vaso-occlusive Crisis (VOC)

Recurrent episodes of acute pain, known as acute pain crisis or VOC, is the most common manifestation and reason for hospital presentation in SCD. Entrapment of sickled RBCs in the microcirculation leads to erythrostasis, obstruction of blood flow, and subsequent tissue ischemia and injury, most commonly in the bone and bone marrow. Almost all people with SCD will experience an acute pain crisis at least once in their life. The pain is most commonly felt in the chest, extremities, and back. Multiple locations are frequently affected simultaneously. Other acute complications of SCD such as acute chest syndrome (ACS), splenic sequestration, and papillary necrosis, can lead to other areas of pain (chest, abdomen, flank).

Although there is no specific diagnostic test for VOC, common clinical findings include joint swelling, weakness, acute anemia, and low-grade fever. These episodes of acute pain can be so severe that hospital admission is necessary for pain control. Pain crises may be precipitated by dehydration, skin cooling, infection, emotional distress, hypoxia, and menstruation, but often no underlying cause is identified. Recurrent bouts of acute pain crises lead to the development of chronic pain, which has both mental and physical consequences. Individuals suffering from chronic pain in SCD can develop anxiety, depression, or chronic opioid dependence.

Multisystem organ failure (MSOF) is a severe complication in SCD associated with VOC. Rapid deterioration and eventual failure of the lungs, liver, and/or kidneys can be seen. Fever, rapid drops in hemoglobin and platelets, and encephalopathy are clinical hallmarks.[1,5]

Acute Chest Syndrome

ACS is a complication of SCD that presents clinically very similar to pneumonia, often with cough and fever. Symptoms such as pain in the extremities and dyspnea are more common in adults. It is the second most common cause of hospitalization in SCD after

acute pain crises and is the leading cause of death in adults. It can develop during a hospitalization for VOC or after a surgical procedure and can be prevented with frequent incentive spirometer use.

Diagnostic criteria include a new segmental radiographic infiltrate with at least one of the following findings: fever (temp >38.5 C), >2 percent decrease in SpO2 from a steady state value on room air, PaO2<60 mmHg, retractions or accessory muscle use, oxygen requirement, tachypnea, chest pain, rales, wheezing, or cough.

The etiology of ACS can be infectious (bacterial, viral, mixed), bone marrow pulmonary emboli, intrapulmonary sickling, atelectasis, pulmonary edema, or infarction. Co-morbid lung disease and a prior history of ACS increases the likelihood of recurrent episodes. ACS must be treated rapidly and aggressively as it can progress to acute respiratory distress syndrome (ARDS) or MSOF. Neurologic complications such as altered mental status, seizures, and neuromuscular abnormalities have also been reported in patients with ACS.[1,6,7]

Initial management includes pain control, fluid management to avoid hypovolemia, broad spectrum antibiotics, supplemental oxygen, bronchodilators, simple blood transfusion or exchange transfusion, and venous thromboembolism (VTE) prophylaxis.

Acute Anemia

Nearly all people with SCD have some degree of chronic anemia. Baseline hemoglobin levels vary based on hemoglobin genotype and from individual to individual. When assessing acute anemia, it is important to keep the "baseline" value for a patient in mind. In general, individuals with sickle cell anemia (HbSS or HbS β0-) have a baseline hemoglobin of 6-8 d/dL, individuals with HbSB+-thallessemia have a baseline of 9-12 g/dL, and those with HbSC have a baseline of 10-15 g/dL. Patients with sickle cell anemia can tolerate lower levels of hemoglobin because tissue oxygenation is relatively preserved when not in the acute vaso-occlusive phase.

In acute anemia (defined as a decline of at least 2 g/dL in hemoglobin), the reticulocyte count is important to measure in order to help determine the cause of the drop. Etiologies of acute anemia include: hemolysis (sometimes from hemolytic transfusion reactions or infection), sequestration of RBCs in the spleen, lungs, or liver, or aplastic crisis. In cases of anemia associated with peripheral destruction, the reticulocyte count will increase as a physiological bone marrow response. Aplastic crisis is the sudden and acute drop in hemoglobin, sometimes to life threatening levels, due to the arrest of erythropoiesis. Markedly reduced reticulocytes in the peripheral blood are seen. It is often associated with parvovirus B19 infections and management is with supportive transfusions.

Hemolytic anemia in patients with SCD can lead to hyperdynamic circulation, expanded plasma volume, dilated cardiomyopathy at an early age, jaundice, and an increased incidence of pigmented gallstones.[1,5]

Splenic Sequestration

The spleen is one of the first organs to be affected in SCD. Splenic sequestration refers to the trapping of RBCs and platelets in the spleen, leading to splenic enlargement, sometimes associated with infarction and pain. There is usually an accompanying worsening of anemia and thrombocytopenia, and leukopenia can also be seen. Hyposplenism may eventually occur, leading to increased susceptibility to encapsulated microorganisms such as Streptococcus pneumoniae. Splenic sequestration can be acute or chronic, with acute sequestration associated with life threatening anemia.[1,5]

Sepsis

Increased susceptibility to infection in patients with SCD, particularly to encapsulated organisms, is secondary to a combination of factors: reduced or absent spleen function, defects in complement activation, micronutrient deficiencies, and tissue ischemia. Of particular significance are infections caused by Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenza (H. influenza), and Salmonella species. Fever in SCD must be taken seriously with prompt evaluation. It can sometimes be a harbinger of other complications such as VOC with or without infection, ACS, or osteomyelitis. Pneumonia, urinary tract infections, hepatobiliary infections, and osteomyelitis are the most frequently encountered infections.[1,4]

Initial management includes a history and physical exam to look for signs of localization, a complete blood cell count with differential, reticulocyte count, and blood cultures. Empiric parenteral antibiotic therapy is recommended. Cephalosporins (e.g., Ceftriaxone) are commonly used, and Vancomycin can be added in cases of suspected meningitis or septic shock. Azithromycin can be added in suspected ACS. Other tests to consider depending on the clinical situation include urine analysis and culture, chest X-Ray, and lumbar puncture.

Stroke

Compared to the general population, individuals with SCD have an increased risk of both ischemic and hemorrhagic strokes, which may be preceded by transient ischemic attacks (TIAs). Hemorrhagic strokes are associated with a higher mortality rate, and tend to occur in young adults, whereas ischemic strokes are more common in adults age 35-65. Stenosis or occlusion of the internal carotid or middle cerebral artery is often implicated, but acute stroke can also be precipitated by ACS, parvovirus infection, or other causes of acute anemia in SCD. Risk factors for stroke include HbSS genotype, increasing age, hypertension, and lower baseline hemoglobin.

Ischemic strokes tend to present with hemiparesis, while headache with altered mental status and seizures are more commonly seen with hemorrhagic stroke. The treatment of stroke in patients with SCD includes targeted therapies such as exchange transfusion, but workup of modifiable risk factors such as diabetes or hypertension should also take place.[1,8]

Acute Kidney Injury

Acute kidney injury (AKI) can occur in individuals with SCD secondary to renal papillary necrosis. Obstruction of blood flow by sickled RBCs leads to medullary infarction. Signs and symptoms can include: a rise in serum creatinine and reduction in glomerular filtration rate, decreased urine output, flank pain, and hematuria. Repeated bouts of acute kidney injury can lead to chronic kidney disease and end stage renal failure.[1]

Musculoskeletal/Orthopedic

Avascular necrosis (AVN), also known as osteonecrosis or aseptic necrosis, is caused by diminished blood supply to the bone resulting in bone infarction and death. RBC sickling causes occlusion of blood flow at the capillary level particularly at the distal portion of a bone near a joint. The femoral head is most often involved. The humeral head and other joints such as the tarsal bones, ribs, skull, and mandible are less commonly affected. Risk factors include certain genotypes (HbSS, HbSS-α-thalassemia, HbSβo-thalassemia), age, frequency of acute pain episodes, and hemoglobin level. Pain with weight bearing is the most common presenting symptom, although some patients can be asymptomatic. AVN can lead to rapid deterioration and eventual femoral head collapse requiring surgical intervention. Workup of suspected AVN should include imaging.

Individuals with SCD are also at risk for osteomyelitis, particularly from Salmonella infection, which is an unusual cause of osteomyelitis in the general population but is seen in the sickle cell population. Staphylococcal infections are still the most common cause of bone infections in patients with SCD. Similar to bone infarction, osteomyelitis may present with pain, fever, and localized swelling.[1,11]

Lower extremity ulcers are a common and debilitating complication of SCD. The pathogenesis of leg ulcers involves obstruction by sickled RBCs of the microvasculature, arteriovenous shunting depriving the skin of oxygen, decreased NO, and excessive vasoconstriction in dependent positions. Trauma, infection, male sex, increased age, and low baseline hemoglobin levels are risk factors for ulcer formation. The ulcers typically form on the ankles, and deep ulcers can lead to osteomyelitis. Chronic pain is a sequelae of recurrent or severe ulceration.[1,12]

Priapism

Priapism is a sustained, painful erection lasting longer than 4 hours, and can affect up to 35% of boys and men with SCD. Stuttering priapism refers to multiple episodes of painful erections lasting less than 4 hours and can be a warning sign for a more sustained event. The vaso-occlusive/low flow type of priapism, termed ischemic priapism, is most common. Urgent evaluation by a urologist is needed. Untreated or repeated bouts of priapism can lead to impotence.[1,9]

Hepatobiliary Complications

SCD can affect the hepatobiliary system either directly via vaso-occlusion or indirectly from hemolysis of RBCs or repeated blood transfusions. Biliary complications include acute cholecystitis, cholelithiasis, cholodocholithiasis, biliary sludge, acute hepatic sequestration, acute sickle cell hepatic crisis, and acute intrahepatic cholestasis.

Increased hemolysis leads to elevated unconjugated bilirubin levels, which can precipitate the formation of gallstones and biliary sludge. This can lead to acute cholecystitis, cholelithiasis, choledochotlihiasis, biliary duct dilation (with or without gallstone formation), and gallstone pancreatitis. The presenting signs and symptoms are similar to when these diseases occur in the non-SCD population.

Sickled RBCs can get trapped in the liver, compressing the bile ducts and leading to pooling of blood within the liver. This is termed acute hepatic sequestration. It is associated with acute anemia (2 g/dL or greater drop in hemoglobin) and enlargement of the hepatic capsule which causes right upper quadrant (RUQ) pain.

Acute sickle cell hepatic crisis presents with RUQ pain, low grade fever, and vomiting, with associated leukocytosis, elevated transaminases, and conjugated bilirubin. It is caused by stagnation of sickled RBCs within the liver sinusoids leading to decreased blood flow through the liver. A rare complication of sickle cell hepatic crisis is hepatic infarction.

Acute intrahepatic cholestasis is a rare but potentially fatal complication in SCD. It can be viewed as a severe form of sickle cell hepatic crisis, with stasis, hypoxia, and intracanalicular cholestasis secondary to ballooning of the hepatocytes. Severe hyperbilirubinemia, coagulopathy and thrombocytopenia, and even liver failure can be seen. Presenting symptoms include RUQ pain with extremely tender liver, light colored stools, and jaundice.[1,13]

Ocular Complications

Patients with SCD are at risk for acute ocular complications such as central retinal artery occlusion (CRAO), hyphema (blood in the ocular anterior chamber), orbital and peri-orbital infections, orbital infarction, and orbital compression syndrome.

CRAO presents with painless, sudden, unilateral or bilateral blindness, and is due to thrombus forming in the artery. Orbital infarction typically occurs during a VOC and leads to inflammation of the infarcted bone which can cause protrusion of the eye, eye pain, and lid/orbital edema. Proliferative sickle retinopathy (PSR) and vitreous hemorrhage are chronic ophthalmological complications in SCD and are more common in individuals with HbSS or HbSC. PSR is associated with significant vision loss.[1]

Key Points:

- Vaso-occlusion leads to recurrent episodes of acute pain most commonly in the chest, back, and extremities. It is the most common cause of hospitalization for patients with SCD.
- ACS is a complication in SCD that can present similar to pneumonia, with cough, fever, and shortness of breath. It is the second most common cause of hospitalization and not as the leading cause of death in adults with SCD. It must be treated promptly and aggressively.
- Chronic anemia is almost universally seen in patients with SCD, and episodes of acute anemia can be caused by hemolysis, RBC sequestration, or aplastic crisis.
- Other pathophysiologic manifestations of SCD hospitalists must be aware of include stroke, splenic sequestration, sepsis, acute kidney injury, orthopedic issues, priapism, hepatobiliary, and ocular complications.

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CHAPTER TWO

Triage and Initial Medical Management

Patients with SCD presenting for care are evaluated as other patients but with special attention to their unique risks and complications.

The Emergency Severity Index (ESI) triage system, which takes into account risk, severity, and likelihood of resource utilization, is used by more than half of EDs in the U.S. The ESI suggests that persons with SCD be triaged as ESI level 21, which is a very high priority and indicates the need for rapid treatment. Triage emphasis should be on identifying the presence of uncomplicated pain episodes that will require fast and specific initiation of pain management, versus symptoms of a complicated SCD-related illness, such as fever, hypoxia, severe jaundice, or priapism, which will require further evaluation and testing in addition to pain management. A thorough history and physical exam pertinent to the presenting complaint with a special emphasis on the unique complications of SCD is warranted. Initial laboratory testing is most often focused on assessment of hemolysis and the degree of worsening anemia. Complete blood count (CBC), total and direct bilirubin, and lactate dehydrogenase will help evaluate for the presence of intra-and extra-vascular hemolysis. A CBC will assess the degree of anemia. Measuring the reticulocyte count will measure the bone marrow response to anemia and whether it is appropriate, since bone marrow response to acute hemolysis typically leads to an increase in the reticulocyte count. The lack of reticulocytosis may indicate an aplastic crisis or bone marrow suppression, which raises the possibility of parvovirus infection. Baseline values for all of these tests are helpful in the interpretation, as chronic derangements are typical. In patients with cardiopulmonary symptoms, a low threshold for imaging of the chest is useful to evaluate for ACS. As with all patients, high value testing depending upon the initial history and physical is most important.

An important element in the management of patients with SCD being admitted to the hospital is a plan for co-management with hematologists. Practices for this co-management relationship will vary between different institutions. However, developing a local standard for best practices is essential. There are opportunities to more reliably consult hematologists to support management of inpatients with SCD. Commonly with uncomplicated VOC, hospitalists will notify primary hematologists of the admission. Hematology involvement is greater for complications of SCD. In particular, decisions about transfusion type and transfusion targets are usually made in close consultation with hematologists.

Various protocols to initially manage analgesia have been described in patients with VOC. These, and other aspects of pain management, will be discussed in a later chapter.

Acute Chest Syndrome

ACS remains the leading cause of death for adult patients with SCD. ACS requires prompt evaluation and therapy to prevent deterioration and death. Several aspects of care for a patient with ACS require prompt attention; analgesia, oxygen support, blood transfusion, fluid management, and antibiotics. Analgesia must be balanced with sedation to avoid hypoventilation.

Transfusion is a mainstay of therapy for ACS. It should be considered in any patient with the following triad: pulmonary infiltrates/consolidations, significant supplemental oxygen requirements from their baseline, and respiratory symptoms, including chest pain, and shortness of breath. Exchange transfusion is usually preferred to avoid volume overload and hyperviscosity. However, simple transfusion with a goal of Hb of 10 g/dL or up to 1 g/dL higher than their baseline, if severe anemia, can be temporizing if exchange transfusion is not feasible.

It is important to avoid volume overload and possible pulmonary edema. However, in the first 24-48 hours patients will typically require more than maintenance intravenous fluid due to increased insensible losses. Empiric antibiotic therapy should be aimed at likely pathogens which include atypical organisms (chlamydia and mycoplasma), H. Influenza, and S. pneumonia. The recommended regimens are a third-generation cephalosporin and a macrolide antibiotic or a respiratory quinolone.

Transfusion

The use of transfusion therapy in SCD is based on specific indications. Transfusions are generally not indicated in uncomplicated VOC episodes.[6] When they are used, leukocyte reduced and RH and Kell negative RBCs are recommended. The most common indications for transfusion therapy are prophylactic perioperative transfusion, transfusion in the setting of acute complications such as stroke, MSOF, ACS, and chronic transfusion as primary and secondary prevention of stroke in children and adults. The benefit of transfusion is weighed against the common transfusion side effects of alloimmunization, autoimmunization, iron overload, hyperviscosity, and hemolysis (acute and delayed).

In a simple transfusion, the patient receives donor RBCs, whereas in an exchange transfusion, the patient receives donor RBCs while an equal amount of their blood is removed. The benefits of exchange transfusion are related primarily to the removal of sickle erythrocytes and the lower risk of iron overload. Exchange transfusions increase the percent of normal (donor) hemoglobin (HbA)-containing erythrocytes remaining after transfusion, permitting transfusion of increased volumes of donor blood without increasing the hematocrit to levels that excessively increase blood viscosity. The goal is generally to reduce HgbS levels to less than 30 percent. Exchange transfusions also reduce the net transfused volume, which limits iron overload. However, potential risks of exchange transfusion include increased donor unit exposure and subsequent alloimmunization, higher costs, the need for specialized equipment, and the frequent need for permanent venous access.

In general, for patients with SCD with acute anemia (Hb > 2 gms below baseline or less than 6 g/dl hgb, along with severe symptoms referable to the anemia), a simple transfusion should be considered.

Simple transfusion should be considered in the following clinical scenarios:

- Support for hemolytic, sequestration (liver, spleen), or aplastic crises
- Replacement of blood loss
- Treatment of worsening anemia
- Pre-surgery optimization of Hgb levels if blood loss is expected

On the other hand, exchange transfusion is indicated in the following scenarios:

- ACS
- Stroke (acute treatment and prevention)
- MSOF
- Stuttering priapism
- Recurrent, refractory pain episodes (as regularly scheduled transfusions)
- Surgery requiring general anesthesia
- Congestive liver disease
- Complicated pregnancy

Supportive Therapies For Hospitalized Patients with SCD

In addition to adequate analgesia, National Heart, Lung, and Blood Institute (NHLBI) guideline-based therapy supports other interventions.[6] In euvolemic adults with VOC who are not taking adequate fluids by mouth, administer maintenance intravenous fluids. If itching is a side effect with the administration of opiates, prescribe oral antihistamines every 4-6 hours as needed.

Expert panels recommend administering oxygen if room air saturations are less than 95%.[6] Hydroxyurea should be continued during acute hospitalizations, unless cytopenias or sepsis are present. Iron chelation therapy has not been studied in the setting of an acute painful episode, but pathophysiologic studies suggest it may reduce micro-infarction and thus may be beneficial to continue at hospitalization. L-glutamine and Voxelotor can typically be continued throughout hospitalization.

SCD is a thrombophilic state and the use of chemical veno-thromboembolic prophylaxis is recommended, although no randomized controlled trials (RCTs) directly address this specific patient population.[7] The use of an incentive spirometer to prevent ACS in patients with chest and back pain is supported by a small RCT[8] and is recommended broadly in guidelines. Ambulation, while not supported by direct evidence, is recommended to prevent VTE and ACS. In the acute hospitalization setting there is no clear role for occupational therapy (OT) and physical therapy (PT) consults. Simple physical activity has been demonstrated to be beneficial for shortening hospitalizations and improving pain. PT and OT are beneficial for the chronic musculoskeletal (MSK) complications of SCD in the outpatient setting.

Monitoring Recommendations

No clear, high quality data exist to suggest the ideal monitoring for hospitalized patients with SCD. Since these patients almost always receive opiate analgesia, it is important to monitor sedation with a standardized protocol. Pulse oximetry or telemetry should be used for patients on PCA, though primary data on which is superior do not exist. Most guidelines do suggest using a standard scale to track pain and assess vital signs every four hours at a minimum.[6] In addition to evaluation of end organ damage or signs of infection, lab monitoring is often considered central to the care of the hospitalized patient with SCD. It may be important to monitor electrolytes, renal function, and white blood cell counts on a daily basis; however, this decision should be independent of the presence of SCD and based on high-value care principles. Laboratory markers of hemolysis and bone marrow response are often checked frequently during the hospitalization of a patient with SCD. There is no evidence to support this practice. Baseline derangements of the usual markers of hemolysis limit the utility of following these lab values in the acute setting. Indirect bilirubin and lactate dehydrogenase (LDH) are characteristically elevated at baseline for patients with SCD due to chronic extravascular hemolysis. Anecdotal evidence suggests that a profoundly elevated LDH may indicate severe disease, but there is no clear evidence for monitoring of LDH during hospitalization.

Treatment of pain should begin even while evaluating alternative causes of pain. 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. Pain management must be guided by patient report of pain severity. Pain management will be guided by the patient's report of pain severity.

Key Points:

- SCD patients should be triaged with high priority in EDs.
- Patients need to be thoroughly evaluated for conditions that may not be related to SCD as well as unique complications of SCD.
- Initial laboratory assessment needs to focus on an assessment of hemolysis and degree of anemia.
- Broad spectrum antibiotics should be started promptly in patients with ACS (third-generation cephalosporin and a macrolide antibiotic or respiratory quinolone).
- Transfusion therapy is the mainstay of ACS.
- Transfusion therapy in SCD is based on specific indications.
- The benefit of transfusion is weighed against the common transfusion side effects of alloimmunization, autoimmunization, iron overload, hyperviscosity, and hemolysis (acute and delayed).
- Incentive spirometry is recommended to prevent ACS.
- Daily lab monitoring should be based on high value care principles and performed only if it will impact management decisions.
- Careful attention should be paid to sedation level for patients on PCA.

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CHAPTER THREE

Pain Management

Assessment of Pain in Sickle Cell Disease

Many hospitalists have heard a variety of perspectives, oftentimes conflicting, on how to treat pain in patients with SCD. Unfortunately, this frequently translates to the undertreatment of pain in these patients. The most important rule of treating pain in SCD is to **believe the patient**. Objective factors such as vital signs, physical exam findings, or laboratory tests, either alone or in combination, cannot reliably be used as a surrogate for VOC pain.[1] Common pitfalls include incorrectly pointing toward a lack of hemolysis or a stable (or normal) hemoglobin level as justification for withholding medications for pain. In addition, hospitalists may view a lack of vital sign abnormalities, such as tachycardia or hypertension, as an indication that patients do not have physiologically significant pain. This is a widely taught practice that may have applicability in certain disease processes. Patients with SCD, however, frequently have episodes of pain and/or high rates of chronic pain (indeed, pain in these patients is the "rule" rather than the "exception"). Therefore, some degree of habituation, as well as atypical coping mechanisms, is common.[2] Patients with acute and chronic pain due to SCD may not display "classic" objective signs of pain, and subjective reports of pain should serve as the hospitalist's primary, if not only, guidepost in pain management.

Similar to other painful conditions, validated pain scales are useful in estimating pain intensity in patients with SCD. The most widely used in the inpatient setting is the Numeric Rating Scale (NRS),[3] in which patients are asked to rank their pain on a scale of 0 to 10, in which 0 represents no pain at all and 10 represents the worst pain imaginable. Such scales are limited by a high rate of interindividual variability (for example, at a pain level of 6, one person may be writhing in bed, while another may be lying comfortably, asking to be discharged).[4] Therefore, they are not as useful in estimating the absolute value of pain as they are in the difference in pain level in response to treatment. A substantial decrease in pain level, even if the absolute value remains high, could indicate that pain medicine is effective. For example, if a patient's pain level drops from a 9 to 6 after administration of IV morphine, the delta of 3 is much more informative than the absolute values of 9 or 6 alone.

Another major limitation of pain intensity scales such as the NRS is that they do not assess multidimensional aspects of pain, including the functional impact of pain. Patient-reported outcome tools, such as the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me), are multidimensional and allow patients to quantify the impact of pain on daily functioning and behavior.[5] The questionnaire addresses the cognitive, emotional, social, and physical impact of disease, with questions such as, "In the past 7 days, how often did you have trouble remembering things people had just told you?" and "In the past 7 days, how often were you very worried about needing to go to the hospital?" Because the ASCQ-Me asks patients to reflect on the prior 7 days, they are typically used in the outpatient setting to reflect pain management in a longer-term context, and in clinical trials. However, the scale has also been found to be useful in the inpatient environment, though it is certainly not widely used in this setting. Still, hospitalists can use the concepts included in the ASCQ-Me to assess pain in a functional context. For example, they may ask patients on rounds how their pain affects their ability to walk, complete activities of daily living, or engage in their commonly enjoyed activities (such as talking on the phone, reading, or playing games) while in the hospital. Such additional history allows for a more comprehensive evaluation of pain that would not be captured in a numerical pain scale alone.

Quality and character of pain should also be assessed. Neuropathic pain is common in adults with SCD, but may be underestimated.[6] If present, therapies directed at neuropathic pain should be used. Importantly, hospitalists should also elicit the patient's perspective on other aspects of the presenting

pain, such as whether the pain episode is typical or atypical in location and quality, any precipitating factors, and other accompanying symptoms. Any pain that is atypical should prompt the hospitalist to consider other causes of pain besides VOC pain, including infection or ACS.

Individualized Care Protocols

The use of individualized care plans for patients with SCD has been shown to be effective in both treating pain and decreasing healthcare utilization. In a pediatric sickle cell study, staff developed "individualized pain plans" for all patients presenting to the ED, which included pain management regimens for the home, ED, and inpatient setting, as well as individual preferences for anti-nausea or anti-pruritic medications.[7] After instituting this practice, there was a decline in length of stay (LOS) and hospital readmissions relative to a national cohort. Individualized pain plans also resulted in higher patient satisfaction and improved pain control.

In a study of adult patients with SCD with high healthcare utilization, a multidisciplinary team created patient-specific care plans that were entered into the medical record as best practice advisories.[8] Care plans included specific opioid regimens that were previously successful, including Patient-Controlled Analgesia (PCA) settings, as well as prior sickle cell emergencies, behavioral issues, and transfusion history. After implementation, there was a decrease in all healthcare utilization measures studied, including ED visits, ED LOS, hospitalizations, and inpatient LOS. Another study of high-utilizing adult patients with SCD implemented similar individualized protocols, with additional details about social history and utilization patterns, which were uploaded into the electronic health record.[9] Post-implementation, there was a decrease in hospitalizations and readmissions by about 50%. There was also a nearly 50% decrease in inpatient costs.

In the context of strong evidence for the efficacy of patient-specific care plans, expert consensus now recommends treating patients presenting for pain with individualized protocols, or at least SCD-specific protocols, whenever possible.[1] Ideally, care plans should be developed with input from patients, families, and clinicians (nurses, ED clinicians, primary care physicians, hospitalists, and hematologists), and should be available in the medical record so all members of the care team can consult and follow the plan. Because care plans are most commonly developed in the outpatient setting, hospitalists generally do not take an active role in their development. It is critical, however, that hospitalists seek out and follow individualized care plans as much as possible.

Management of Acute Pain

Many acute pain episodes are treated successfully at home, either with non-opioid medications or oral opioids in combination with hydration and rest. For severe pain, many patients present to outpatient day hospitals or infusion units, which are dedicated to the management of uncomplicated VOC pain. Day hospitals have been shown to reduce ED visits and admission rates, decrease LOS, and save healthcare costs.[10–12] However, day hospitals are typically only open during daytime hours and are not widespread across the country.[13] For many patients, the ED is often the only option for management severe pain.

Typically, by the time patients have presented to the ED, oral opioids and supportive measures have failed. Therefore, in general, patients with SCD who present to the emergency room with a chief complaint of pain should be treated aggressively with parenteral opioids. The U.S. and U.K. have released evidence-based guidelines for the management of acute pain episodes in patients with SCD.[1,14] In a paper titled "Evidence-Based Practice Standard Care for Acute Pain Management in Adults With Sickle Cell Disease in an Urgent Care Center," Kim and coauthors outline a specific pain management protocol that is in accordance with these guidelines.[15]

Patients presenting to the hospital with severe VOC pain require prompt (within 30 minutes) administration of parenteral opioids.

Oral opioids alone are not appropriate because they cannot provide adequate analgesia rapidly enough. Morphine or hydromorphone are typically first-line therapies, though fentanyl is preferable in the setting of hepatic dysfunction. If an individualized care plan or medication administration information from prior hospitalizations is not available, it is reasonable to start with 0.1-0.15 mg/kg of morphine (maximum initial dose 10mg) or 0.02-0.05mg hydromorphone (maximum initial dose 1.5mg). However, if possible, the dosing of parenteral opioids should be guided by what provided effective analgesia during previous visits (this information is likely found in a patient's individualized care plan, if one exists). A recent study found that guideline-based analgesia with patient-specific opioid dosing resulted in greater improvements in pain compared to a weight-based strategy, without increased side effects.[16]

Rapid and frequent re-assessment of pain is crucial. Pain intensity, mood, functional capabilities, and level of sedation should be assessed 15-30 minutes after a parenteral dose of an opioid analgesic. A pain intensity reduction of roughly 50% on the upper end of the pain scale is considered adequate. If pain remains uncontrolled, consider escalation of dose by 25%.

Round-the-clock opioid administration is recommended over on-demand or PRN opioids. Several small studies suggest that patient-controlled analgesia may be the most effective method for providing such round-the-clock pain management. One study, which compared PCA with intermittent IV morphine in the ED, showed that patients receiving PCA had a shorter elapsed time between onset of pain and treatment.[17] In a randomized controlled trial comparing PCA to continuous IV morphine, patients receiving PCA had significantly lower cumulative morphine consumption with similar mean daily pain scores.[18] In addition, there was a nonsignificant trend toward decreased LOS in the PCA group. A hospitalist-led management of patients with vaso-occlusive pain crises using a care pathway that emphasized early, aggressive PCA-based pain control was associated with reduced inpatient LOS.[19]

PCA pain management can be offered in two different modalities. In a demand-only setting, the patient has the option to self-administer a preset amount of IV opioid by pressing a button. In the demand plus continuous infusion setting, in addition to the demand dose, a present dose is scheduled to be delivered over an hour period and repeats hourly. Home doses of long-acting oral opioids should be concurrently given if demand-only PCA settings are used. One study found that using demand-only PCA in conjunction with long-acting home oral opioids was associated with shorter LOS, likely because it eliminates the need to transition the patient from intravenous to oral pain medications when pain is improved. [20] If prior effective PCA settings are not known, hospitalists can use the one-time opioid doses that were known to be effective in the ED to guide how much to provide per hour through the PCA pump.

As with all diseases characterized by severe pain, achieving adequate pain control in patients with SCD may be difficult, and some patients continue to report pain despite high doses of opioids. Hospitalists should strongly consider enlisting the help of other clinicians in this case. In our experience, a specialized pain management service, if available, is almost always helpful in co-managing pain. Some institutions recommend consulting the pain management service on any patient receiving doses of opioids that exceed certain morphine equivalent daily doses (MEDD). At the institution of two authors, that threshold is an MEDD of 90mg. In addition, hospitalists should consider involving outpatient providers, including primary care doctors and hematologists, for help in co-managing patients' pain. These clinicians may be able to provide valuable insight into what has worked for patients in the past.

Resolution of pain may occur after 24-72 hours, but varies significantly among patients, and in the same patient during different vaso-occlusive pain crises. One study found that acute pain can last as long as a few weeks, though the mean duration was 5 days (range 1-40).[21] Upon resolution of acute pain, clinicians can begin to taper opioids to home doses, and parenteral opioids can be converted to oral formulations.

The patient should be discharged on a home opioid regimen that is similar if not identical to the pre-admission regimen. Patients who are not discharged with opioids have higher rates of hospital readmission compared to those that are discharged with oral opioids.[22]

In deciding which type and route of pain medications to provide, hospitalists should take patient preference into account in determining which opioid to use, since variation in individual drug metabolism may lead to improved efficacy of certain opioids compared to others. Indeed, some authors have stated that, "Patients should be acknowledged as experts and collaborated with in developing an appropriate plan of care."[23]

Non-Opioid Pain Management

In addition to opioid analgesics, guidelines recommend the use of NSAIDs and acetaminophen if there are no contraindications.[1,14] Although as many as 25-40% of patients with SCD experience neuropathic pain, current guidelines do not incorporate recommendations for neuropathic pain.[24] Neuropathic pain should be managed according to standard guidelines. Ketamine, which has been shown to be effective in certain types of neuropathic pain, is emerging as a potential treatment for VOC pain. Small case series have shown that it can improve symptoms in opioid-refractory pain, and may reduce the need for opioids.[25,26] The feasibility of using Ketamine is likely to be limited to local expertise and the availability of specific protocols. In our experience, Ketamine can only be written by a pain management specialist.

Non-Pharmacologic Pain Management

In the hospital setting, opioids are not only the cornerstone but often the exclusive method by which pain control is achieved. However, hospitalists should have an awareness of non-pharmacologic strategies that have been shown to be beneficial in this disease. Psychological response is fundamental to the experience of pain, and maladaptive coping strategies, including negative thinking, somatization, and catastrophizing can worsen an individual's pain experience.[27] Several studies have explored the use of psychological therapies, including education and support groups, relaxation techniques, self-hypnosis, and cognitive behavioral techniques to improve coping skills and alleviate the global experience of pain.[28] One review found that long-term training in cognitive-behavioral techniques, including biofeedback, hypnosis, and cognitive-behavioral therapy (CBT), are "probably efficacious" in reducing SCD pain.[29] Certain electronic health interventions, which employ smartphones or tablets to provide CBT training, may help decrease self-reported pain in children and adults with SCD.[30,31]

Existing guidelines make little reference to specific psychological strategies in the setting of acute pain management. British guidelines recommend that clinicians, "Encourage the patient to use their own coping mechanisms (for example, relaxation techniques) for dealing with acute pain." There is insufficient evidence to guide the use of specific psychological interventions as a non-pharmacologic pain control strategy in the acute inpatient setting.[28] In the long term, however, an emphasis on psychological therapies to improve pain coping skills and social support could decrease patients' reliance on opioids. Psychological interventions can be incorporated into care plans and may reduce the need for emergency and acute care.[27]

Aside from psychological-based interventions, other non-pharmacologic strategies may have a role in treating pain. A small study found that deep tissue pressure specialized neuromuscular massage therapy (NMT) appeared to have a beneficial effect on pain in SCD.[32] Other strategies may include heat pads and acupuncture.[27] Cold packs should not be used since they may precipitate sickling.

Substance Use Disorder in SCD: Fact versus Myth

Because patients with SCD present to the hospital frequently with pain complaints, often with specific requests for opioid regimens that have worked for them in the past, physicians often incorrectly assume that such patients are drug-seeking, exaggerating pain, or have an opioid-use disorder. [33–35] Alarmingly, in one study, 86% of clinicians in academic centers did not accept that patient self-report is the best metric for pain in patients with SCD.[33] Compounding this is the fact that Black patients, who make up the vast majority of patients with SCD, are more likely to be suspected of opioid abuse.[36]

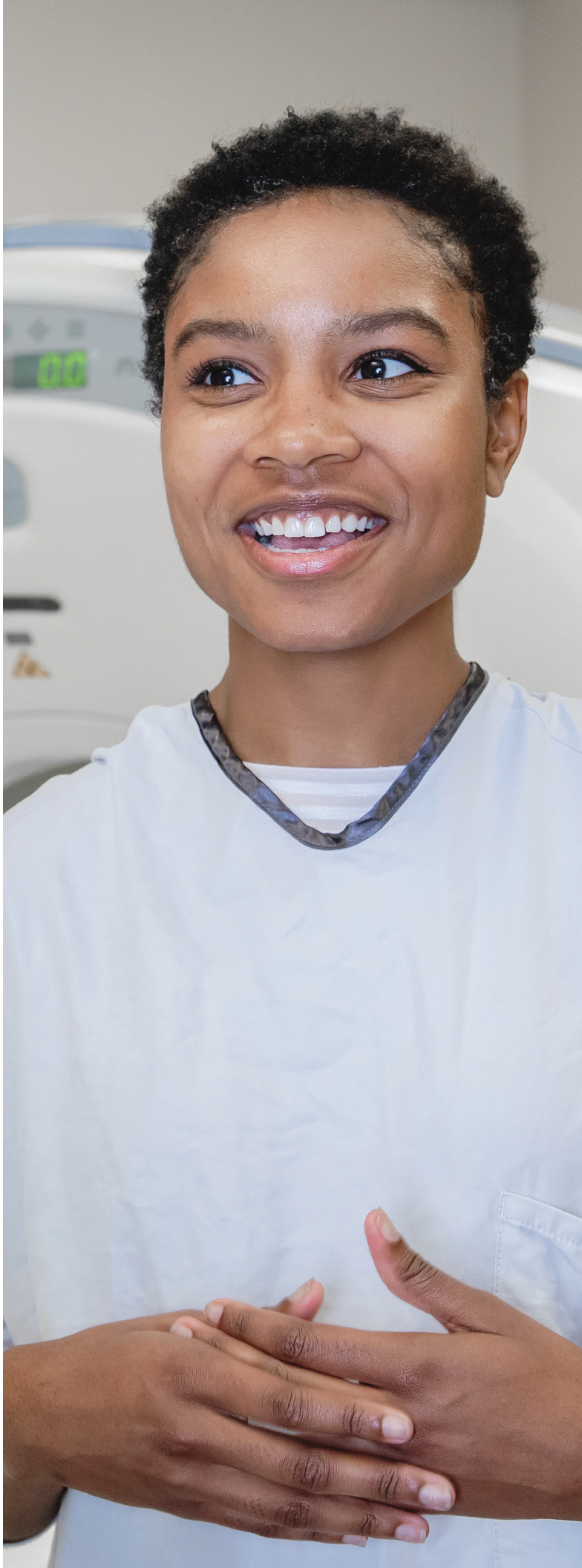
Assumptions about drug-seeking behavior lead to mistrust between physicians, patients, and family members, which may result in delayed and inadequate treatment for patients in pain. In reality, drug-seeking behavior and opioid addiction in patients with SCD is rare. One study found an incidence of opioid use disorder to be 8.3%, which is similar to or below that of the general population.[37,38] A more recent study found that 0-22% of patients with SCD on chronic opioids were misusing or at-risk for misusing opioids, but neither of the scales used in the study were validated in a SCD population.[39] More commonly, patients with SCD exhibit signs of pseudo-addiction, which resembles drug addiction but is actually caused by under-prescription of drugs to treat pain, causing them to seek more.[40] Furthermore, physiologic dependence, manifested by tolerance and withdrawal symptoms, is expected in patients with SCD with long-term opioid use. Hospitalists should be careful to distinguish these entities from true addiction. They should also be aware that stigmatizing or biased language (i.e. "patient is a sickler", "patient refused", "patient is narcotic-dependent") used in the medical record may adversely affect attitudes and prescribing behavior of other physicians. Neutral language should be used whenever possible.[41] In light of the stigma and systemic racism that many patients with SCD face throughout their lives, our view is that patients should be given "the benefit of the doubt" whenever possible.

Concurrent use of cannabinoids is common in adults with SCD.[42] Medical marijuana is now legal in many states, but in others it is still considered an illicit substance. Though a percentage of patients with SCD use marijuana recreationally (sometimes with other illicit substances, most commonly cocaine and phencyclidine), the majority endorse marijuana use for chronic pain, weight loss and anxiety management.[43] Research on the efficacy of marijuana in pain management in SCD is lacking.

Illicit substance abuse in patients with SCD has been reported. In a small study, the Prescription Opioid Misuse Index (POMI) was able to identify patients with SCD at risk for opioid abuse.[44] Paradoxically, patients who are not adequately treated may develop an addiction to opioids or cocaine as they self-medicate to treat their pain.[45] This provides further rationale to ensure adequate pain control in patients with SCD. Cocaine use has been documented in patients with SCD and may be associated with increased risk of VOC.[46] There are no specific evidence-based recommendations for referring patients with possible substance abuse to appropriate treatment. Hospitalists may consider outpatient referrals to social work, addiction medicine, or psychiatry on a case-by-case basis.

Key Points:

- The most important pain management principle in SCD is to believe the patient. Objective markers cannot be used as a surrogate for pain.
- Pain that is not typical for a patient's usual VOC pain should prompt evaluation for an alternative cause, including infection or ACS.
- Individualized care plans, which contain specific opioid regimens that have been previously been successful, should be followed when available.
- Upon presentation the ED, pain should be treated promptly (within 30 minutes) with parenteral opioids.
- Round-the-clock opioid administration is recommended over on-demand or PRN opioids. PCA may be the most effective method for inpatient pain control.
- Acetaminophen and NSAIDs may be used in addition to opioid analgesics if there are no contraindications. Ketamine, which has shown some benefit in opioid-refractory pain, is an additional option if available.
- The incidence of opioid-use disorder among patients with SCD is frequently overestimated by healthcare providers.



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CHAPTER FOUR

Transitioning From Intravenous Opioids

Upon resolution of acute pain, clinicians can begin to taper opioids to home doses, and parenteral opioids can be converted to oral formulations.

There are no formal guidelines for transitioning off IV opioids (including PCA) for patients with SCD. Hospitalists should consider following general guidelines for the management of chronic pain.[1,2] The standard approach outlined in these guidelines involves four steps:

1) Calculate the patient's total opioid requirement over the past 24 hours.
2) Convert the total daily opioid requirement to an equivalent amount of a short-acting oral opioid, preferably one that will be used upon discharge.
3) If transitioning to a different opioid, consider decreasing the total opioid equivalent by 25-50% to account for incomplete cross-tolerance.
4) Divide the daily dose into "as needed" doses of a short-acting opioid, or, if appropriate, divide the daily dose into equal amounts of short- and long-acting opioids.

Another option, described by a recent small observational study, is to add an "oral tier" of opioids to a PCA regimen once pain control is achieved.[3] In this protocol, the oral tier consists of 3 orders. The first is for an oral opioid to be administered every 3 hours on a scheduled basis, while giving the patient the option to decline. The other two orders allow for additional oral opioids in escalating doses for moderate or severe pain. Nurses can withhold doses at their discretion in the setting of opioid-related adverse events, such as sedation or respiratory depression. Once the oral tier is initiated, patients are encouraged to use the oral tier as opposed to PCA demand doses. Over the next few days, the PCA can be transitioned off. This and other similar strategies have had anecdotal success, though head-to-head studies are lacking.

There are several other well-accepted best practices for tapering opioids in the inpatient setting, including:

- Avoid tapering opioids within the first 24 hours of hospital admission
- Make dose adjustments during the day, when staffing is higher and clinicians can more easily respond to uncontrolled pain
- Decrease the dose of opioids, as opposed to increasing the interval in between doses
- When decreasing doses, taper by 10-20% at a time
- Convert to oral opioids when the IV dose is roughly equivalent to home doses

Opioid Prescriptions at Discharge

Patients who have been treated with opioids in the hospital should have similar (if not identical) doses of opioids available to them upon returning home, and often will require prescriptions from hospitalists. Studies have identified a lack of opioid prescription at discharge as an independent risk factor for readmission in both children and adults.[4,5] It is best practice to prescribe opioids to the hospital pharmacy during daytime hours to ensure that patients leave the hospital with appropriate medications in hand. In some cases, filling opioid prescriptions at community pharmacies may prove challenging, particularly when prescriptions are for high quantities and doses of opioids.

Non-Opioid Prescriptions at Discharge

In general, SCD therapies should be continued as an inpatient when possible. If home medications have been held for clinical reasons, they should be held on discharge and resumed by the patient's hematologist when appropriate. Hydroxyurea, in particular, should be held during hospitalization in the setting of severe cytopenias or overwhelming infection. It should not be resumed at discharge but may be restarted at post-discharge follow-up.

Follow-up Planning

Once a patient has improved and is deemed stable for hospital discharge, careful consideration must be paid to effective outpatient handoff and timely follow-up appointments. A review of the literature shows there is currently no widely validated discharge checklist for the SCD population. Patients with SCD are at particularly high risk for readmission to the hospital. A retrospective study looking at 21,112 patients with SCD from 2005-2006 found that the 14- and 30-day rehospitalization rates were 22.1% and 33.4% respectively. These readmission rates are high even when compared to other complex diseases such a type 1 diabetes, spina bifida, cystic fibrosis, and IBD.[7]

It is important to communicate a safe and clear discharge plan with patients, families, and caregivers. A study examining risk factors for readmissions found that up to 57% of adult patients felt they were not healthy enough to leave the hospital during their index admission. The most common reason for readmission was uncontrolled pain. Other common risk factors for readmission include forgetting follow-up appointments, having an appointment scheduled at an inconvenient time, or not having transportation. This underscores the importance of the engagement of a multidisciplinary team with case managers and social workers during hospitalization and at the time of discharge. Other potentially modifiable risk factors for readmission include mental health issues, financial problems, and spiritual issues, which should be addressed if possible.[8] Limiting barriers to discharge and providing clear discharge instructions are crucial in trying to limit rehospitalizations.

Outpatient follow-up with a primary care provider (PCP) is important in preventing readmissions. The absence of a PCP and lack of follow-up within 14- or 30-days is associated with a higher risk of readmission.[5,9] Caring for a patient with a complex disease such as SCD requires knowledge on screening and prophylaxis guidelines, SCD complications, and pain control. Often a hematologist assumes the role of a PCP in this patient population, although an internist or family practitioner with experience in treating SCD is also an option. As a patient with SCD ages, they might be best served having both a PCP to deal with chronic medical issues, as well as a hematologist to address SCD specific problems.

Timely follow-up with a PCP and hematologist should be arranged prior to hospital discharge (ideally within 14 days) and patient factors that could lead to missed appointments should be addressed. Having timely and regular follow-up with a PCP also helps ensure that patients with SCD get referrals to other specialties if needed, such as ophthalmology, pain management, psychiatry, and social work.

Key components of a safe discharge include:

- Agreement between patient, family, and care team that discharge is appropriate (pain is controlled on oral medications, and there are no outstanding medical issues that need further work-up or treatment)
- A thorough discussion of discharge medications, and full medication reconciliation
- A plan for how to address new or worsening symptoms after discharge: when to come to the ED versus when to call the patient's PCP
- A follow-up appointment within 1-2 weeks with the patient's primary SCD physician, and any other subspecialty appointments, as applicable
- Transportation arrangements for follow-up appointments, if required

Individual Patient Care Plans

Individualized care plans offer an approach for patients to avoid unscheduled care and facilitate ED and hospital care when necessary. **Key aspects include:**

- Plans for self-management at home, with specific attention to pain medication management
- When to escalate care in the setting of exacerbations or crises
- ED care instructions, including specific medications and dosing
- Inpatient care, with specific medications and dosing
- Pain contracts, if appropriate
- Follow-up plans that address specific issues such as transportation for follow-up appointments

Multiple institutions, including academic and larger community hospital systems, have published on the impacts of individualized care plans.[10–13] They were all based on patient-specific best practice advisories embedded within electronic medical record systems, and were all developed by multidisciplinary teams. These teams consistently involved inpatient and outpatient internists, emergency medicine, psychiatry or psychology, social workers, case management, and nurses. One group also included risk management representation on their intervention team.[8] Another group specifically involved addiction psychiatry.[13] Most studies found a reduction in inpatient days and ED visits.[10,11,13] One study found that readmissions were significantly decreased[12], and another demonstrated that the number of ED visits where a patient left prior to receiving treatment was reduced, suggesting enhanced care delivery.[13]

Key Points:

- Close attention should be made to transitioning patients to an effective oral pain regimen.
- Patients with SCD are at increased risk of rehospitalization at 14- and 30-days.
- The multidisciplinary approach used during the patient's hospitalization must be continued at the time of discharge, with clear discharge planning communicated by all members of the care team.
- Risk factors for rehospitalization include forgetting about or not having scheduled follow-up appointments, lack of transportation, inadequate pain management at discharge or lack of supply of prescription pain meds, mental health issues, and financial problems.
- Outpatient follow-up with a PCP and hematologist arranged prior to discharge can help reduce hospital readmission.
- Patients with SCD are very likely to have unmet social needs, and should be addressed when possible.
- Multidisciplinary teams should create care plans focused on home self-management of pain crises, plans for ED visits, and inpatient treatment.

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Conclusion.

The chronic and potentially debilitating nature of SCD can pose significant challenges for the inpatient management of this patient population. A multidisciplinary hospital team comprised of hospitalists, hematologists, case management, social work, nursing, and pharmacy must work together collaboratively to improve outcomes for these patients. Patients with SCD face physical, psychosocial, and socioeconomic challenges. Chronic pain with acute painful episodes is a prominent feature of SCD and opiate therapy is a mainstay of treatment, though there is it often stigma for patients with SCD who rely on opioids. Given the chronic and recurrent nature of SCD, patient-centered care plans can be used to facilitate judgement-free and efficient care. Because of the complex nature of the disease and the likelihood of readmission to the hospital, there is an opportunity to improve transitions of care for patients with SCD. The patient's objectives should be considered to create better outcomes.

Many aspects of this disease call for further study. Discharge readiness is generally dependent on subjective assessments by patients and providers and there currently is no standard checklist or assessment to assist in guiding this decision making. There is an opportunity to better define discharge-related best practices in order to facilitate effective transitions of care. Given the high prevalence of unmet social needs in patients with SCD, particular attention must be given to social determinants of health. Prevalence of social determinants of health has been understudied in the adult population with SCD. Better definition of the social issues of this population may aid in development of support systems.