

Frequently Asked Questions by Hospitalists Managing Pain in Adults With Sickle Cell Disease

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Pain is the predominant medical presentation to hospitalists for patients with sickle cell disease (SCD). Dramatic treatment gains of SCD in childhood have resulted in more adults now requiring hospitalization than children. This has created new challenges to improve the quality of hospital care for SCD. The evidence base for pain management in SCD is lacking. We therefore offer some evidence and our informed opinion to answer frequently asked questions (FAQs) about pain management by hospitalists caring for adults with SCD. The most common questions center around defining a crisis; selecting and managing opioids; distinguishing between opioid tolerance, physical dependence, and addiction or misuse; determining appropriateness of discharge; and avoiding lengthy or recurrent hospitalizations. *Journal of Hospital Medicine* 2011;6:297–303. © 2011 Society of Hospital Medicine.

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Severe, disabling pain, often requiring opioids, is the most common medical presentation for children and adults with sickle cell disease (SCD), an autosomal recessive red blood cell disorder affecting those of African, Mediterranean, and Asian descent.^{1,2} A genetically controlled hemoglobin alteration impairs oxygen binding, and enables polymerization of deoxy-hemoglobin, resulting in, classically, sickle-shaped erythrocytes³ and a complex cascade of ischemia and vaso-occlusion in the microcirculation.^{4,5}

Dramatic gains in the treatment of SCD in childhood have resulted in markedly improved survival through adulthood.^{6–8} Thus, the need for adult SCD care is relatively new and rapidly growing. In 2005, approximately 70% of the nearly 80,000 US SCD hospitalizations occurred in adults versus children (Table 1). These hospitalizations occurred in the context of a poorly coordinated American health care system,⁹ despite the hopes raised by the Patient-Centered Medical Home¹⁰ and the Chronic Care Model.¹¹

Adults with SCD are vulnerable both because they are usually members of racial and ethnic minority groups, and because they have a Food and Drug Administration (FDA)-defined “orphan” disease.¹² They often do not receive the only FDA-approved medication for SCD, life-saving hydroxyurea,¹³ recommended for adults with homozygous sickle cell anemia (Hb SS) and sickle- β^0 thalassemia (Hb S β^0 Thal).¹⁴ Young adults often fail to experience a smooth transition of care from children’s hospitals, falling into a medical abyss.¹⁵

Therefore, increasingly, hospitalists are managing adults with SCD, rather than adult hematology–oncology, pain, or palliative care specialists. Adults with SCD experience negative opinions, bilateral lack of trust, and conflict in the doctor–patient relationship, frequently cited in studies of SCD adults and providers in the literature.^{16,17}

Evidence Base

General guidelines for SCD management have been published by the National Institutes of Health (NIH)¹⁸ and the Agency for Healthcare Policy and Research.¹⁹ But one of us (K.L.H.) found evidence lacking with regard to SCD pain management.²⁰ Published guidelines on general pain management, such as the World Health Organization’s Analgesic Ladder,²¹ do not address SCD. A Cochrane Review of pain management in SCD found only 9 randomized controlled trials, all with small numbers of patients, addressing acute SCD pain only.²² As well, American and British consensus SCD pain guidelines^{23,24} admit, and subsequent publications emphasize,^{25,26} the lack of evidence for what to do or not do for SCD pain management. At least 1 well-done summary of the SCD evidence base intended for hospitalists has been published, but it focuses on management of issues other than pain.²⁷

Motivations and Fears

It is not surprising then that hospitalists may bring great fear and apprehension with them into their care of SCD

patients. One of us (W.R.S.), a general internist, has been called by his own and 3 other academic medical centers, 2 with active Federally-funded SCD research programs, to address the problems of high-utilizing adults with SCD, including counseling hospitalists frustrated with the management of pain in these patients.

Hospitalists may be motivated to provide efficient inpatient management (Table 2), and be aware of pain as the primary symptom of SCD inpatients. But they may carry knowledge gaps and biases into their relationships with SCD inpatients. They may fear opioid administration (opiophobia), loss of licensure or governmental reprisals because of

high-dose prescription of opioids, or may believe that SCD patients are more often addicted than most.^{17,28} Consequently, more troublesome hospital stays may occur when patients are not rapidly and adequately titrated to appropriate analgesic doses, or when unnecessary deleterious side effects result from opioid and other analgesics. We therefore offer answers to frequently asked questions (FAQs) about pain management by hospitalists caring for adults with SCD. We address FAQs arising during the prototypical situation—a patient with SCD admitted for a painful exacerbation, and little or no acute comorbidity. We refer the reader to the aforementioned articles and guidelines to address other treatment issues in adults with SCD.

TABLE 1. Adult and Pediatric Admissions for Sickle Cell Disease,* 2005 and 2008

	2005			2008			
	Total No. of Discharges		LOS	Total No. of Discharges		LOS	
All discharges	79,187	100.00%	5.3	70,121	100.00%	5.4	
Age group	<1	996	1.26%	2.5	513	0.73%	2.7
	1-17	23,134	29.21%	3.9	13,754	19.62%	3.8
	18-44	48,168	60.83%	6	48,021	68.48%	5.8
	45-64	6,527	8.24%	6	7,543	10.76%	5.6
	65-84	281	0.35%	6.4	221	0.32%	5.6
	Missing	81	0.10%	4	70	0.10%	3.0

NOTE: Data extracted from the Healthcare Cost and Utilization Project database, <http://www.ahrq.gov/data/hcup/>.

Abbreviations: LOS, length of stay in days (mean).

* International Classification of Diseases, Clinical Modification (ICD-CM) principal diagnosis code(s) 282.60, 282.61, 282.62, 282.63, 282.64, 282.69.

FAQS

1. Is there any objective way to tell when SCD patients really are in a crisis?

Although the term “crisis” is used as if it were an objectively definable biological entity, no one has proposed a standard definition of a “crisis” based on pain intensity level, clinical features, or biomarkers. Measures of vaso-occlusion are correlated with ischemic pain, including pain that is often called a “crisis.”^{29–32} However, neither ischemic pain from SCD, nor the underlying vaso-occlusive cascade that is associated with this pain, is a sudden, present-or-absent phenomenon. Instead, these are continua that can be measured using pain scales or various biomarkers.

There is, however, correlative evidence of the intensity of SCD pain associated with various distinctive health states (admitted/not admitted, in “crisis”/not in “crisis”). The most visible measure of a “crisis,” health care utilization,

TABLE 2. General Motivations and Principles of Efficient Inpatient Sickle Cell Pain Management, and the Obstacles to Inpatient Care of Sickle Cell Disease

Principle	Obstacles
Make appropriate management handoffs for patients coming from the ED to promote continuity of care and shorten hospitalization	Poor information systems and poor handoffs/continuity from ED management to hospital management
Get as much preexisting information about the patient as possible to inform acute care, avoid returns or further hospitalization	Patient may have no primary care physician or may underutilize primary care
Provide rapid and adequate analgesia	Patient may misuse ED and hospital (as primary care source)
Don't lose licensure or arouse regulatory suspicion about prescribing patterns	Ignorance of the differences between tolerance, physical dependence, addiction, and pseudoaddiction
Get the patient discharged as soon as medically appropriate	No specific data on pharmacodynamics of opioid analgesics in sickle cell disease
Make appropriate handoffs with the patient's usual source of continuity care (provide that source when necessary) to avoid returns or further hospitalization	Ignorance of DEA monitoring and laws governing appropriate vs inappropriate prescribing of opioids
Define and maintain appropriate roles for hospitalists vs physicians with sickle cell training, pain specialists, or other specialists	Difficulty assessing pain quality and intensity
	Difficulty assessing/avoiding side effects of analgesics
	Difficulty determining appropriateness/timing of changes in analgesic dosing, discharge planning
	Patient may have no primary care physician or may underutilize primary care physician
	Patient may be mis/underprescribed analgesics by primary care physician
	Inadequate adult system of care for sickle cell disease (no/paucity of specialty care)
	Multiple prescribers of opioids
	Providers unwilling to care for or prescribe opioids for sickle cell patients

Abbreviations: DEA, Drug Enforcement Administration; ED, emergency department.

was a strong predictor of mortality in the Cooperative Study of Sickle Cell Disease. Patients with 3 or more admissions per year had a lower 5-year survival rate.³³ In contrast, “crisis” in the landmark Pain in Sickle Cell Epidemiology Study (PiSCES) was self-defined by patients.³⁴ Despite being in pain on over half of their days on average, and despite a third of patients being in pain daily, most pain in PiSCES was not considered a “crisis,” and less than 5% of patients’ days were spent in emergency departments (EDs) or hospitals. Ambulatory pain intensity reports were correlated with opioid use.³⁵ A substantial minority (35%) of PiSCES patients made at least 3 ED visits per year. However, these high ED utilizers had worse laboratory values, more pain, more distress, and a lower quality of life.³⁶

Importantly, sometimes adults with SCD may have severe comorbidities which may not be addressed or may be mistakenly managed as an acute vaso-occlusive episode without further investigation or timely specialist consultation. Although pain is primarily the individual’s chief complaint, any potential relationship between the presence of medical comorbidities and pain should be examined when patients are admitted.

2. How can one know when opioid dosages should be changed, or when SCD pain is appropriately controlled to allow discharge?

We recommend, as a standard of care, that SCD pain assessment and pain therapy be interwoven, despite a systematic review finding no evidence that directly linked the timing, frequency, or method of pain assessment with outcomes or safety in medical inpatients, and concluding that the safety and effectiveness of patient-controlled analgesia (PCA) in medical patients had not been adequately studied.³⁷ Hospitalists should focus the first 24 hours of inpatient SCD pain management on cycles of recurrent pain assessment and opioid dose titration as frequently as every 1 to 2 hours, to assure safe and rapidly efficacious analgesia. Pain intensity, duration, and character should be assessed directly. Intensity is often assessed using a visual analog scale (VAS) or numeric rating scale.³⁸ Treating physicians should themselves directly assess pain during discussions of therapy with the patient, even though some assessment usually is done in hospitals during each nursing shift. Pain and pain relief can be assessed indirectly by monitoring opioid use.

We recommend PCA for inpatients with SCD, administered as an intermittent demand dose (patient must push a button) of opioid, with or without a background opioid constant infusion.³⁹ We usually set the interval between doses, or “lockout,” to 6 to 10 minutes. Both the lockout and the sedation from delivered doses prevent patients from pushing the demand button repetitively to the point of overdose. Use of a low-level constant infusion (“basal”) may sustain pain control during times when the patient is asleep, avoiding recrudescence of pain and “lost ground” due to inadequate analgesia during rest. Alternatively,

long-acting oral opioids may be continued if already used at home, or newly introduced to provide adequate baseline pain control which is augmented by the demand dosing. Most PCA pumps monitor hourly opioid dose demand (number of pushes), as well as hourly doses delivered. Both hourly opioid dose demand and hourly dose-per-demand ratio are measures of PCA efficacy or futility. Pumps record this data, and can be interrogated at the patient’s bedside for up to several days of prior use. Physicians should combine pump interrogation with direct pain assessment to guide demand-dose titration. Demand doses should be increased to 1.5 to 2 times the previous demand dose after several hours of failed reduction of pain intensity and duration, and/or persistently futile dose-per-demand ratios.

PCA interrogation is also useful for conversion of parenteral opioids to oral opioids, as well as to guide the recommendation for discharge home. After the first 24-48 hours of up-titration, if opioid dose demand decreases concordantly with pain frequency and intensity, the demand dose may be safely decreased, and eventually daily PCA requirements may be summed and converted to oral medication using standard opioid dose conversion tables. At this point, physicians may use single measures or daily averages of directly assessed pain.

Routine PCA use in SCD is backed by some evidence.^{40,41} But we find it important that patients be taught and encouraged to use the demand feature of PCA. Still, for various reasons, some patients do not use PCA pumps well. Discordant or unreliable assessments (eg, high pain intensity but low-opioid demand doses during the same interval) may result, and PCA potentially may fail as a dosing strategy. Management is more difficult for these patients. One alternative dosing strategy is prescription of scheduled doses of a short-acting opioid, attaching to each dose the order, “patient may refuse.” This is different than dosing “as needed,” and allows counts of dose refusals over an interval, analogous to PCA pump interrogation.

3. How much is too much opioid? Should one rely on side effects, or on requests for medicine, or is there a ceiling dose?

Addictionologists, pain specialists, oncologists, those involved in hospice care, and some hematologists caring for SCD patients agree that, in general, there should be no a priori dose limitations imposed on opioid prescribing for acute pain. Instead, titration of dose of opioid to pain relief is a central principle of acute pain management. Experts also agree that particular opioids carry particular side effects which warrant dose limitation, adjustments, or avoidance of that opioid altogether. A summary of opioids commonly used in SCD, along with warnings and implied dose limitations is found in Table 3.

For safety, it is important to assess the history of prior opioid use to recognize a patient who is not tolerant to opioids (see below, FAQ 4), to avoid mistakenly

TABLE 3. Table of Opioids, Frequency of Use, and Special Considerations in SCD

Opioid	Used Frequently (>20% of Patients)	How Used	Unique Side Effects and/or Dose Limitations
Short-acting			
Codeine	No	Inpatient, parenteral; Ambulatory, oral	
Oxycodone	Yes	Most commonly used ambulatory opioid	
Morphine	Yes	Most commonly used inpatient opioid	
Hydromorphone	Yes	Inpatient more than ambulatory	
Fentanyl	No	Inpatient, parenteral	Short-acting
Hydrocodone	No	Ambulatory	
Meperidine	No	Avoided	Unpredictable seizure, coma, death
Propoxyphene	No	Ambulatory	
Tramadol	No	Ambulatory	
Long-acting			
Oxycodone	No	Ambulatory and as an oral "basal" in inpatients	Abuse potential from capsule manipulation
Morphine	Yes	Ambulatory and as an oral "basal" in inpatients; most commonly used long-acting opioid	
Methadone	No	Ambulatory and as an oral "basal" in inpatients	Dose-dependent prolongation of QT _c , torsades de pointes
Fentanyl	No	Ambulatory and as a transdermal "basal" in inpatients	Abuse potential from transdermal patch manipulation

Abbreviations: SCD, sickle cell disease; QT_c, corrected Q-T interval on electrocardiogram.

overdosing a patient using doses often required by tolerant patients. In lieu of a pre-written, individualized opioid dosing plan in place for the patient, the patient may be the best source of information regarding preferred medication and tolerated doses.

The reader is referred to standard texts for a description of opioids, their pharmacokinetics and pharmacodynamics, and their addictive and abuse potential. The side-effect profile of opioids is well-known: nausea, vomiting, and itching frequently occur; hallucinations, respiratory suppression, and myoclonus occur infrequently.⁴² Meperidine may more readily cause central nervous system (CNS) dysfunction, including seizures, as compared to other commonly used opioids, because of its toxic metabolite normeperidine. Use of meperidine is often avoided, especially use via PCA.⁴³ Methadone may cause dysrhythmias, specifically corrected Q-T interval (QT_c) prolongation and torsades de pointes on an electrocardiogram, in doses above 200 mg per day.⁴⁴ Some recommend baseline and yearly electrocardiogram monitoring when giving methadone chronically.

Recognizing the potential dangers of opioids, it is also reasonable to look for opioid-sparing analgesic strategies. Non-opioid analgesics such as ketorolac⁴⁵ and adjuvants such as ketamine⁴⁶ that are opioid-sparing should be considered whenever feasible. Complementary and alternative therapies such as transcutaneous electrical nerve stimulation (TENS)⁴⁷ have less evidence of effectiveness, but have limited risks and may be of use for some individuals.

4. What are the major signs of substance abuse (opioids, street drugs) in SCD patients already on opioids, and can a hospitalist judge those signs acutely and intervene appropriately?

Reports of underprescription of opioids in SCD have cited physician fear of abuse and addiction.⁴⁸ A recent informal poll of adult sickle cell providers suggests policies vary on how potential abuse is monitored in ambulatory sickle cell patients. We note that physicians, especially upon meeting a patient for the first time, may be unable to reliably judge whether that patient is abusing opioids or street drugs. Both false-positive and false-negative diagnoses may be made.⁴⁹ Repetitive reports of lost or stolen prescriptions or pill bottles, receipt of prescriptions from multiple providers, or repeated requests for early refills increase the suspicion of misuse or abuse, but are indirect evidence. Urine and serum monitoring may be useful, but may give incorrect information if misinterpreted or not conducted frequently enough to improve sensitivity.⁵⁰

It is important to distinguish between tolerance, the decreased analgesic response over time to repeated doses of the same drug; physical dependence, the production of withdrawal upon abrupt discontinuation of an opioid agonist or administration of an antagonist; and addiction, the psychological dependence upon opioids. Tolerance may be misperceived as true addiction. Its earliest symptom is shortening of the duration of effective analgesia. In contrast, addiction may be manifested by dose escalation in the absence of an increased pain stimulus, or by use of opioids for purposes other than pain relief.⁵¹ These are not easily distinguished during a single patient encounter.

SCD patients' requests for specific opioid medications in specific doses, should not be taken as evidence of past or current abuse, but rather evidence of a well-informed, self-managing patient. Adults with SCD are clearly expected to be very knowledgeable about and tolerant to opioids if they have had a life of pain as a child, and will

require higher doses of opioids than other patients treated by most hospitalists. The issue of medication abuse may be best handled in the ambulatory setting. Whenever possible, hospitalists should not rely only on data from the acute care setting to manage patients. Ambulatory providers may conduct random, unannounced urine and/or serum testing, as part of an opioid prescribing agreement that is written and filed in the patient's chart. Assays for prescribed opioids (especially long-acting agents), as well as assays for common drugs of abuse, should be conducted. Comanagement with an addictionologist, psychiatrist, or psychologist should be considered in individuals suspected of opioid abuse.

We do not suggest routine urine drug test monitoring of all SCD patients unless routine monitoring is done as a policy for all patients on opioids. Though the prevalence of addiction may be higher in subpopulations of patients with pain,⁵² and though prescription of opioids, prescription drug abuse, and accidental deaths from prescribed opioids have risen exponentially in the last several years,⁵³ in our experience and in the published literature, drug misuse/abuse among SCD patients is no worse than among patients with other illnesses.^{54–56} However, pseudoaddiction, the appropriate seeking of needed opioids from multiple physicians because of uncontrolled pain and opioid underprescription, may well be prevalent in SCD,⁵⁷ and may be mistaken for true addiction.

5. How can patients' readiness for discharge be assessed? What can be done for the patient who has lengthy and/or multiple hospitalizations or frequent ED visits?

The appropriate time for discharge in most patients is when they can manage their pain at home with oral opioids or less. Often, patients do not improve even after a few days of inpatient therapy.⁵⁸ A typical pain episode may last much longer than the 6-day average US hospital length of stay for a diagnosis of sickle cell "crisis" among 18–44 year olds (Table 1).⁵⁹ Patients may return and be readmitted.^{60,61} But in the best cases, pain resolves or reverts to a usual chronic intensity level. As described in FAQ 2, daily or more frequent pain assessment is a bedrock for making discharge decisions. Patients well-experienced in the use of pain intensity scales can report their usual pain intensity at home, and how close they are to their "baseline" pain intensity. Simply asking patients, "Are you ready for discharge?" is appropriate and may yield a surprising positive response. In a recent inpatient trial of PCA (manuscript in preparation), adult patients were admitted with a minimum pain intensity of 45 mm on a 100 mm horizontal VAS scale after treatment in the ED, and mean pain intensity of 76 mm \pm 10 mm. All adults in this study were discharged with pain that was clinically significantly lower. Researchers have found a VAS change of 13.5 mm to be the minimum clinically significant change⁶² during treatment of vaso-occlusive crisis.⁶³

Unremitting pain despite appropriate titration of opioids and prolonged hospital stays suggests the need for com-

prehensive evaluation for medical and psychosocial comorbidities, as is done for other patients with chronic pain syndromes. If not already done, discussion with the patient's primary care provider may reveal factors impacting on persistent pain. Consultation with a hematologist, pain or palliative care specialist, or other provider familiar with SCD may prove helpful. Implementation of adjuvant therapies as discussed in FAQ 3 and adding long-acting oral opioids to continue postdischarge may also help. Hyperalgesia, or heightened sensitivity to pain, is normal after acute tissue injury, but is now suspected in SCD as a long-term neuropathic pain syndrome, as a consequence either of repeated painful crises or of chronic opioid therapy.² Only some centers have specialists qualified to test for and diagnose neuropathic pain.⁶⁴ Discharge planning should include identification of a source of outpatient follow-up. Opioids prescribed at discharge should be sufficient to last at least until the first outpatient appointment, to avoid repeated ED or hospital visits. Communication with a primary care provider at discharge can enhance successful care transition. Otherwise, for patients without established providers, social workers and others may address barriers to follow-up that frustrate both patient and provider.

Support for Hospitalists Managing Adults With Sickle Cell Disease

Beside the general advice on pain management in SCD mentioned above or found in the bibliography of this article, at long last, a group of adult practitioners skilled in the care of SCD has formed nationally. The Sickle Cell Adult Provider Network [<http://www.scapn.net>] provides non-binding advice and support to its members via an e-mail listserve. Topics often include pain management. This advice fills a vacuum created by the lack of evidence-based guidelines.

Ultimately, evidence and updated guidelines will be the best support for hospitalists and others managing pain in SCD. The hope is that SCD will receive the attention it deserves, so that practitioners and patients alike do not suffer continued pain from this disease or its management.

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