

# Sickle Cell Vaso-occlusive Pain Crisis in Adults: Alternative Strategies for Management in the Emergency Department

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**ABSTRACT:** The gene for sickle cell disease is carried by 8% of the African-American population in the United States. The primary care physician is often called upon to recognize and treat one of the major sequelae of sickle cell disease—vaso-occlusive pain crisis. An injectable nonsteroidal anti-inflammatory drug has recently become available and may offer some improvement in outcome of vaso-occlusive pain crises. We present five case reports reviewing various current therapeutic options, including newer pharmacologic agents, and comment on alternatives to inpatient management of pain crises. The use of the emergency department short-term observation unit as an alternative to hospitalization is discussed.

THE GENE for sickle cell anemia is carried by approximately 8% of the African-American population in the United States, the expected incidence of the homozygous state at birth being 1:625.<sup>1,2</sup> With many sickle cell patients now surviving into their fourth decade<sup>2</sup> or longer, the primary care physician is increasingly called upon to manage acute complications of hemoglobin SS disease. One of the most frequent complications encountered in the outpatient setting is the sickle cell vaso-occlusive pain crisis. From the many available treatment methods, management of pain crisis is determined by multiple factors, including subjective pain severity, probability of crisis-associated infection, response to initial analgesia, and past experience of the treating physician.

The following five representative cases were recently seen and managed at the University of Mississippi Medical Center (UMMC).

## CASE REPORTS

**Case 1.** A 26-year-old man with known sickle cell disease (Hb SS) came to the Emergency Department (ED) after 12 hours of lower back and hip pain. His last ED visit had been 2 months earlier. He was afebrile on this admission, and his vital signs were consistent with his usual presentation: temperature 36.8°C (98.4°F), pulse rate 100/min, respiratory rate 20/min, and blood pressure 120/60 mm Hg. Complete blood count (CBC) was normal for him during pain crisis (WBC 24 200/mm<sup>3</sup>, hematocrit value 30.7%).

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An intravenous infusion of 5% dextrose in half normal (0.5 N) saline was started at 175 mL/hr, and the patient received 60 mg ketorolac intramuscularly and 50 mg amitriptyline orally. After 1½ hours in the ED, he was discharged with instructions to (1) push fluids by mouth, (2) take acetaminophen with oxycodone as needed for pain (12 tablets prescribed), and (3) return to the ED if symptoms worsened. His next ED visit for pain crisis was 1 month later.

**Case 2.** A 22-year-old woman with Hb SS disease complained of lower back and retrosternal chest pain for 1 day. Her last ED visit had been 24 days earlier. She was afebrile and her vital signs did not differ from usual during pain crisis (temperature 36.9°C [98.5°F], pulse rate 98/min, respiratory rate 24/min, and blood pressure 110/84 mm Hg). CBC and reticulocyte count were within this patient's range of normal (WBC 10 700/mm<sup>3</sup>, Hct 26.3%, reticulocyte count 8.0%) as compared with laboratory values from previous admissions. Chest roentgenogram and urinalysis were not suggestive of acute infection.

She was initially given 25 mg of meperidine and 12.5 mg of promethazine intravenously, and an intravenous infusion of 0.5N saline was started at 125 mL/hr.

Four hours after presentation to the ED, she was admitted to the ED observation unit, where she remained for 23 hours. During this time she received three doses of meperidine (50 mg) and promethazine (25 mg IV) and one dose of amitriptyline (25 mg orally). Hydration was continued. At the end of this observation period, the pain was significantly improved and the patient felt well enough to go home.

Discharge instructions were to return if symptoms worsened and to take acetaminophen with oxycodone for pain (15 tablets). She next came to the ED 1 month later.

**Case 3.** A 33-year-old woman with Hb SS disease came to the ED because of pain in the arms, legs, back, and chest. Pain had been present since her discharge from another hospital 1 week earlier; she had been hospitalized for 1 week for management of pain crisis. Before this, she had been pain free for several months. On the current presentation her temperature was mildly elevated (38°C [100.5°F]), consistent with her previous pain crises, and other vital signs were normal

for her (pulse rate 120/min, respiratory rate 20/min, blood pressure 110/57 mm Hg). The CBC was also comparable to previous values (WBC 26 900/mm<sup>3</sup>, Hct 21.8%), but the reticulocyte count was 70.0%. Chest roentgenogram and urinalysis were unremarkable.

She was hydrated intravenously with 5% dextrose in 0.5N saline at 150 mL/hr, and she initially received meperidine (50 mg) and promethazine (25 mg) intramuscularly. In the observation unit she received two more doses of meperidine (50 mg) and promethazine (25 mg) intravenously.

Because the pain failed to abate and the reticulocyte count remained high, the patient was admitted to the Internal Medicine Service, where she continued to receive IV hydration and IV narcotics for 2 days. She was then given an oral regimen of acetaminophen with oxycodone and was discharged on the fourth hospital day, with instructions to report to the Sick Cell Clinic for 2 months of follow-up care. Prescriptions were given for folic acid, ibuprofen, and acetaminophen with oxycodone (12 tablets).

**Case 4.** A 17-year-old girl with sickle cell anemia (Hb SS) gave a history of bilateral leg pain for 1 day and a nonproductive cough for 3 days. Her last ED visit was 6 weeks earlier. Vital signs were usual for her during crisis (temperature 36.3°C [97.4°F], blood pressure 110/palpated mm Hg, pulse rate 92/min, respiratory rate 24/min), and CBC and reticulocyte count were consistent with her usual pain crisis presentation (WBC 25 000/mm<sup>3</sup>, Hct 30.0%, reticulocyte count 12.1%). Results of urinalysis were normal. A chest film showed only chronic changes consistent with sickle cell disease.

Intravenous hydration was begun with 5% dextrose in 0.5N saline at 200 mL/hr and she initially received 50 mg of meperidine and 25 mg promethazine intravenously. She was subsequently admitted to the observation unit for 26 hours, during which she received four more doses of meperidine and promethazine over 16 hours, followed by three doses of acetaminophen with oxycodone over a 10-hour period. When left ear pain developed, dullness of the left tympanic membrane was found, and three doses of trimethoprim-sulfamethoxazole (TMP-SMZ) were given because of the possibility of early acute suppurative otitis media. The pain failed to resolve, and the patient was admitted to the Internal Medicine Service with a diagnosis of sickle cell pain crisis complicated by upper respiratory tract infection with left otitis media. During the first inpatient day, her temperature rose to 39.4°C (103°F); TMP-SMZ therapy was discontinued, and treatment with intravenous erythromycin was begun. She continued to receive meperidine and promethazine for 2 days, after which she was given oral oxycodone. She was discharged 1 day later and instructed to return to the Hematology Clinic in 3 weeks. Prescriptions were given for folic acid and acetaminophen with oxycodone (number of tablets not recorded). Her next ED visit was 4 months later.

**Case 5.** A 29-year-old man had pain in the neck, right flank, and right leg for 2 days; he had taken acetaminophen with codeine, without relief. It had been 2 months since his most recent crisis. Physical examination was essentially unremarkable. Vital signs were usual for him on presentation to the ED (temperature 37.3°C [99.2°F], pulse rate 112/min, respiratory rate 28/min, and blood pressure 130/60 mm Hg). CBC was consistent with his previous values (WBC 19 500/mm<sup>3</sup>, Hct 28.9%, reticulocyte count 17.7%), and findings on urinalysis and chest film were within normal limits.

The patient was initially given meperidine (75 mg) and promethazine (25 mg) intramuscularly and amitriptyline (50 mg) orally, and IV administration of normal saline was started at 200 mL/hr. He received an additional 50 mg of meperidine and 25 mg promethazine intramuscularly 1½ hours later.

He was admitted to the observation unit 6 hours after arrival in the ED, and he remained there for 18 hours. He was given one more IV dose of meperidine and promethazine. Two hours later he received 60 mg of ketorolac intramuscularly, with relief of pain for 7 hours. He was then given another 30 mg of ketorolac intramuscularly. Four doses of oral amitriptyline were given during this admission. He was discharged 6 hours after the last dose of ketorolac, with continued resolution of acute pain.

On discharge, he was instructed to return if symptoms worsened and to maintain adequate fluid intake. He was given a prescription for acetaminophen with oxycodone (15 tablets).

His next ED visit for pain crisis was 1 month after discharge.

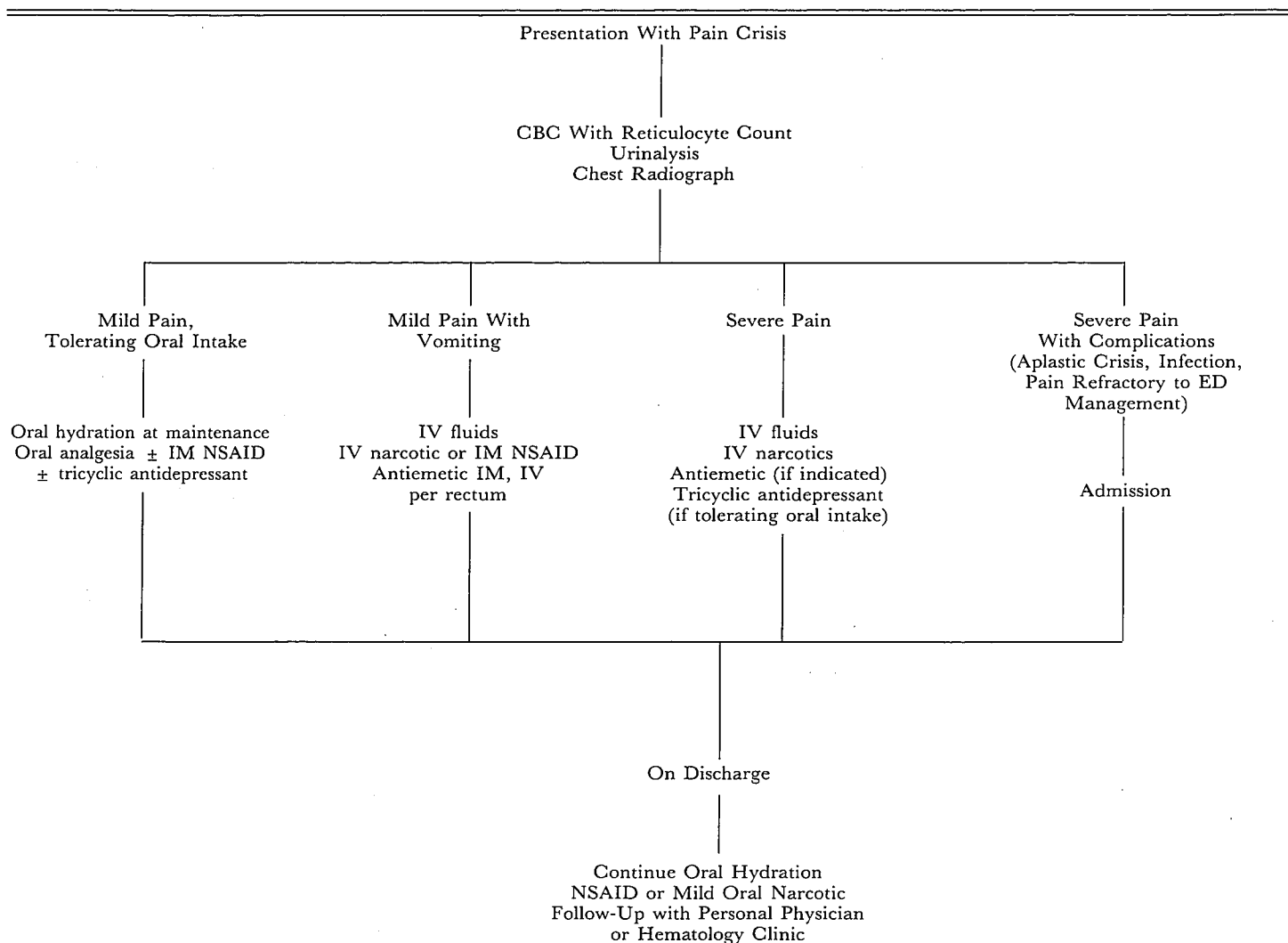
## DISCUSSION

Vaso-occlusive pain crisis is common among patients with sickle cell disease. The pain is believed to be caused by ischemic tissue injury resulting from obstruction of blood flow by sickled erythrocytes. This blockage of flow results in acidosis and regional hypoxia, which increases sickling and causes further injury and pain.<sup>3</sup> The initial insult may be due to a number of precipitating causes, especially infection. Other causes are dehydration, hypoxia, exposure to extreme cold, and any inflammatory condition.<sup>3</sup> The primary care physician is often faced with the task of recognizing and treating this debilitating condition. A search for a reversible precipitant, an important aspect of pain crisis management, should include history, physical findings, and laboratory evaluation. A CBC with reticulocyte count, urinalysis, and chest roentgenogram will not only help to evaluate for infection, but the CBC and reticulocyte count can also aid in detecting aplastic crisis, which can have manifestations similar to those of pain crisis. Dehydration is also a frequent factor in the advent of a pain crisis, and may be suggested by physical examination or urinalysis showing a high specific gravity.

While precipitating factors are being investigated or appropriately managed, the physician must also treat the pain crisis itself. Current therapy includes oral or intravenous hydration, analgesia, treatment of any precipitating events, and supplemental oxygen.<sup>1,3,5,6</sup> One problem always facing the physician is quantification of pain. The sickle cell patient has a complicated pain presentation that may be best described as a chronic pain syndrome complicated by acute episodic pain.<sup>6</sup> Often the only evidence of this pain is patient description, since signs of autonomic nervous system activation may disappear once pain becomes chronic. Unless there is evidence to the contrary, it is recommended that the physician believe the patient's report and aggressively treat his pain.<sup>6</sup>

As illustrated by our cases, effective treatment methods may vary greatly. We routinely obtain

**TABLE. Management of Sickle Cell Pain Crisis**



NSAID = nonsteroidal anti-inflammatory drug.

a CBC with reticulocyte count, urinalysis, and chest film to evaluate for infection and aplastic crisis.<sup>4</sup> As shown by the Table, mild cases may be treated with oral analgesia<sup>7</sup> or an intramuscular nonsteroidal anti-inflammatory drug (NSAID) and oral hydration.<sup>7</sup> If the patient is unable to tolerate oral intake, intravenous hydration is required, with intravenous narcotics<sup>1,3,6</sup> or an intramuscular NSAID. Use of intramuscular narcotics is currently being discouraged.<sup>5,7</sup> Antiemetics may be administered as indicated. More severe episodes have typically required parenteral analgesia and intravenous hydration. Hospitalization may be required if the patient has a crisis-related infection or aplastic crisis, or if the pain crisis does not resolve after an observation period in the ED<sup>2</sup> (in our ED, no more than 24 hours). The definition of a pain crisis as mild or severe is subjective, and depends upon patient report,

physician evaluation, and the ED physician's familiarity with the patient's usual crisis.

Although each of the currently available narcotic analgesics has been used for management of pain crisis, meperidine (Demerol) is most commonly given.<sup>6</sup> Use of NSAIDs for analgesia has also been described.<sup>6</sup> Other articles have discussed oral NSAIDs for mild pain crises. Recent research has anecdotally addressed the efficacy of newly available parenteral NSAIDs.<sup>8</sup> We have had success with the parenteral NSAID ketorolac tromethamine (Toradol). An advantage of NSAIDs is the avoidance of side effects of narcotics, including the potential for respiratory depression and narcotic dependence.

These agents have been combined with amitriptyline (Elavil) based on studies demonstrating efficacy of antidepressants in the management of

chronic pain syndromes.<sup>9-13</sup> It has been suggested that a chronic pain syndrome develops with superimposed acute pain crises of sickle cell anemia. Although the amitriptyline's mechanism of action in the control of chronic pain is unknown, it is postulated to be related to the inhibition of synaptic reuptake of norepinephrine and serotonin.<sup>9,10,12</sup> Although there are currently no data to suggest that amitriptyline has an acute effect, we have noted that the use of amitriptyline decreases the frequency of patient requests for pain medication.

Patients are discharged with instructions to maintain oral hydration, to have follow-up care from their personal physician or at our Hematology Clinic, and to return if symptoms worsen. They are given a prescription for a NSAID or a mild oral narcotic.<sup>3</sup> Although postdischarge use of the prescribed oral agents has not been formally investigated, patient reports indicate that most of the prescription is used in the first 48 hours after discharge and the rest is kept for the next painful crisis. If the pain of a subsequent crisis is unrelieved by oral medication, the patient again comes to the ED.

#### CONCLUSION

Sickle cell pain crisis consists of acute pain superimposed on the chronic pain associated with sickle cell disease. Management of the pain crisis is complicated, but currently consists of hydration, analgesia, and management of any precipitating

factors, as illustrated by the five cases we have described.

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