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HEMATOLOGY eDIGEST



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<p>+ Jerry L. Spivak, MD Professor of Medicine and Oncology The Johns Hopkins University School of Medicine</p>	<p>+ Kwaku Ohene-Frempong, MD Professor of Pediatrics Director, Sickle Cell Program and Comprehensive Sickle Cell Center The Children's Hospital of Philadelphia</p>	<p>+ Cage S. Johnson, MD Professor of Medicine Keck School of Medicine University of Southern California</p>	
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In this Issue...

Sickle cell anemia is a condition virtually synonymous with pain, with the acute painful crisis as its hallmark. The physiology of the sickle cell pain process is well documented: vascular occlusion causes damage (microinfarcts) of the tissues supplied by the occluded vessel. This tissue damage generates a number of inflammatory mediators that initiate an electrical impulse of pain transmitted along peripheral nerves (A alpha and C fibers) to the dorsal horn of the spinal cord. The impulse ascends along the spinothalamic tract to the brain stem, hypothalamus, and thalamus, which is a major relay station of the central nervous system (CNS). The thalamus interconnects reversibly with other centers, most notably with the limbic system and reticular formation (mediators of emotion and memory). At the same time, the CNS inhibits the transmission of the painful stimulus at the level of the dorsal horn via a descending pathway that begins in the periaqueductal gray matter of the midbrain. Eventually the modified electrochemical impulse that started at the site of the vaso-occlusion is sent to the cerebral cortex where it is perceived as pain by the patient.

Pain perception is thus a subjective phenomenon that is the result of a complex interplay among enhancing and inhibiting factors at the level of the CNS. Understanding not only the pathogenesis of acute sickle cell pain but also its impact on prognosis and quality of life justifies an aggressive approach to its management at onset.

In this issue, we review recent literature on the acute sickle cell painful crisis of hospitalized patients: its predictors, precipitating factors, phases, and pharmacologic therapy, including methods of administration and side effects of appropriate analgesics.

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+ **Commentary and Reviews by:**
Samir K. Ballas, MD

+ **Guest Editor of the Month:**



Samir K. Ballas, MD
Director Sickle Cell Program
Thomas Jefferson
University
Department of Medicine
Division of Hematology/
Cardeza Foundation

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Sickle cell disease (SCD) is a quadrumvirate of: 1) pain syndromes; 2) anemia and its sequelae; 3) organ failure; and 4) co-morbid conditions. Pain, however, is the hallmark of the disease and the acute sickle cell painful crisis is the insignia of SCD in general and sickle cell anemia in particular. Acute painful episodes are the most common cause of hospital admissions of patients with SCD. Other types of pain secondary to SCD itself also occur, including chronic pain and neuropathic pain. The incidence, frequency, severity, and distinctive features of these pain syndromes have not been investigated in depth and, except for sporadic anecdotes, the current literature is devoid of such reports.

A second major feature of SCD is heterogeneity - usually latitudinally among patients and less often longitudinally in the same patient. Predicting markers of severity will streamline management of affected individuals. Certain predictors may justify aggressive approach to therapy such as bone marrow transplantation or the initiation of hydroxyurea to toddlers.

"Prevention is better than cure" is an adage that has withstood the test of time. Hydroxyurea has been effective in decreasing the frequency of acute sickle cell painful crises, acute chest syndrome, blood transfusion, morbidity, and mortality of patients with sickle cell anemia. Identifying factors that may precipitate a crisis can provide an avenue for the implementation of early prevention. Physical, emotional, and psychosocial stressors all seem to play important roles in precipitating painful episodes, justifying the establishment of programs to counsel individual patients and their families and to educate them in skillfully coping with these factors. Environmental stressors have also been implicated; however, the literature continues to waver on the role of weather changes and air quality in precipitating painful crises.

Like any other acute illness, the sickle cell painful crisis evolves along certain phases - at least four of which are easily identifiable. Each phase is associated with changes in cellular, hematological, and inflammatory markers of the disease. Knowing these phases and their features provides an objective tool to assess patients in crises and to develop a rational approach to monitor the progression of a painful episode.

The mainstay of management of the acute sickle painful crises continues to be pharmacological in nature. Although new opioids and non-opioid analgesics have been introduced into the pharmacopeia of pain management, many of these, unfortunately, have not been tried in patients with SCD. Along with the advent of new analgesics, there has been progress, albeit limited, in the methods of drug delivery other than the intravenous route.

Finally, side effects of both opioids and non-opioids continue to be a major concern. Side effects of analgesics on the CNS, the heart, lungs, liver, and kidney are of paramount importance and should be looked for diligently.

☰ Predictors of Frequency and Severity of Painful Crises

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Several factors have been proposed as predictors of the clinical expression of sickle cell anemia. Most important among these is the level of HbF, with the publications by Steinberg, Bonds, and Francis & Johnson reporting that the higher the level of HbF, the milder the disease and the less frequent the painful crises. Supporting this conclusion, Ballas et al found that increases in HbF induced by hydroxyurea improved RBC deformability and cellular hydration, while Platt et al reported the highest pain rates occurring in patients with a relatively high hematocrit and low HbF. Focusing on the painful sickle cell crisis in children, Hargrave et al reported that nocturnal hypoxia was associated with the frequency of painful episodes. Ballas et al and Lande et al reported that patients (both adults and children) who have decreased cell deformability and increased number of irreversibly sickle cell and dense cells have mild disease with respect to the painful crisis. Schall et al found that suboptimal serum levels of Vitamin A were prevalent in children with sickle cell anemia and were associated with increased hospitalizations as well as poor growth and hematologic status. Ballas & Lusardi and Udezue & Girshab found that males are hospitalized with acute painful crises more frequently than females.

The key findings from the studies quoted above indicate that there are three sets of factors that predict the frequency and severity of painful crises: genetic, cellular, and environmental. Genetic factors include gender,

HbF level either due to heredity persistence or hydroxyurea and epistatic gene modifiers. Although the number of males was less than females (55 vs 62) in the Ballas & Lusardi study and almost equal in the Udezue & Girshab study, males constituted about 60% and 66% of admissions to the hospital respectively in these two studies. Cellular factors that decrease RBC deformability and increase the number of dense cells in the steady state have a salutary effect, most likely because these are associated with more severe anemia and hence relatively decreased whole blood viscosity. Nocturnal hypoxia and decreased level of Vitamin A (< 30µg/dl) are environmental factors amenable to preventative therapy.

Hydroxyurea has already been found to increase the HbF level and ameliorate the severity of disease in most, but not all, patients who take it. Other agents such as decitabine are candidates for further studies. Cellular factors could be altered not only by increasing the HbF level, but also by rehydration of sickle RBC by Mg or inhibitors of the calcium channel (Gardos effect). Finally, modulation of environmental factors (diet, supplements, oxygen, etc.) are relatively simple and easily applicable methods of therapy.

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Precipitants of Acute Painful Crises

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The onset of acute painful crises is usually unpredictable, with dehydration, physical exertion, emotional upheavals, and exposure to cold or hot weather implicated as precipitants of painful events. Although these are possible predisposing factors, the onset of most painful crises cannot be attributed to any of these obvious events. Gill et al reported that daily mood and stress predict painful events, utilization of healthcare facilities, and work activity in adults with SCD. In a retrospective study, Smith et al found a complex relationship between temperature changes/extremes and emergency department visits and hospital admissions for sickle cell painful crises in adults.

Gill et al examined the extent to which daily mood and stress were associated with pain, healthcare use, and work activity in 41 adults with SCD. Analyses of daily diaries indicated that increases in stress and negative mood were associated with increases in same-day pain, healthcare use, and work absences. Bi-directional relationships were also noted, with evidence that pain may be the more powerful initiating variable in pain-mood and pain-stress cycles. Positive mood was associated with lower same-day and subsequent-day pain, as well as fewer healthcare contacts. The most relevant finding of the study by Smith et al was an inconsistent confirmation of a relationship between daily ambient temperature and emergency department visits or hospital admissions for sickle cell crises.

Given the unpredictable nature of painful crises, the identification of precipitants may be helpful to both patients and providers in their attempts to manage pain. The study by Gill et al has important implications for studies of pain management interventions, indicating that stress and mood management may be important additions to cognitive-behavioral pain management programs. The study of positive mood may help researchers discover ways to promote positive psychological well-being and thereby contribute to optimal adjustment to SCD. The study by Smith et al adds fuel to the ongoing controversy on the role of climatic factors as precipitants of acute painful crises that require admission to the Emergency Department and/or the hospital; however, specific prospective longitudinal epidemiologic studies are needed to definitively characterize the relationship between ambient temperature and sickle cell painful episodes and utilization of health resources.

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☰ Phases of the Sickle Cell Painful Crisis

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Jacob et al described the pain experience of children with SCD who were hospitalized for vaso-occlusive painful episodes. The pain experience and signs and symptoms prior to admission and during hospitalization were presented in the context of whether there is evidence to support the existence of phases to a vaso-occlusive painful episodes. Their study was triggered by previous reports by Ballas & Smith, Ballas, Akinola et al and Breyer et al indicating that the acute painful crisis did indeed evolve along phases in adults and children with SCD.

Ballas & Smith and Akinola et al independently and almost simultaneously described the presence of two phases of the painful crisis in prospective longitudinal studies of adults with SCD. Akinola et al studied 20 patients over 16 months and Ballas & Smith studied 117 painful crises affecting 36 patients with sickle cell anemia over 6 years. Both studies indicated the presence of two phases. The initial phase was associated with increasing pain, decreased RBC deformability, increases in the number of dense cells, RDW, HDW, reticulocyte count, leukocytosis and decrease in the number of platelets. The second phase was characterized by established pain of maximum severity and gradual reversal of the abnormalities of the first phase. Later Ballas revised the description of the painful crisis and refined its evolution into four phases by including the observations of several other investigators. The phases were called predromal, initial, established, and resolving phases, respectively. Beyer et al found that the painful crisis also evolves along phases in children but the phases were broken down into seven and were labeled differently. Jacob et al studied 40 crises affecting 27 children over 9 months. Their findings supported previous observations related to changes during the evolution of painful episodes that may be occurring in phases. Although the phases were given different names, the concepts were similar.

The evolution of the painful crisis along phases dispels the notion that there are no objective signs of its occurrence. Serial determination of certain lab parameters with comparison to steady state values clearly reveals the presence of objective lab data describing the crisis. Moreover, the presence of phases allows the provider to monitor the progress of the crisis and manage it according to a rational basis, thus avoiding the conflicts that often arise between patients and providers about the authenticity of pain.

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Opioid and Non-opioid Analgesics

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Recent years have witnessed a plethora of information about both opioid and non-opioid analgesics, with the safety and efficacy of these drugs questioned, re-evaluated, and monitored. Most important among these were the Cox-2 inhibitors, with rofecoxib (Vioxx®) withdrawn from the market due to risk of myocardial infarction, and the safety of other Cox-2 inhibitors as well as the conventional NSAIDs questioned (Hippisley-Cox & Coupland; Solomon et al). A novel non-opioid analgesic called ziconotide (Prialt), derived from the venom of the *Conus magus* snail, has been approved for the intrathecal use in severe chronic pain (Staats). In the opioids arena, Palladone®, a long-acting formulation of hydromorphone, had rapid exit within six months after it came into the market because of evidence that the once-a-day pills could be fatal to patients who take them with alcohol (FDA.Alert). Morphidex® (morphine sulfate/dextromethorphan) was found not to be better than morphine alone (Galer et al). Oxymorphone extended release (ER) tablet formulation seems to be useful to treat chronic pain due to osteoarthritis (McIlwain & Ahdiel). Depodur®, a formulation of multivesicular liposomes containing morphine sulfate, was approved for intrathecal use in patients with severe pain (Viscusi et al). However, none of these drugs has been studied in patients with SCD, nor has comparison of formulation of controlled release opioids (MSContin®, Oramorph®, Avinza®, Kadian®, and Oxycontin®). Recent publications (with mostly anecdotal or quasi-randomized reporting) pertinent to the painful crisis have discussed the use of iloprost (Ilomedin®), magnesium sulfate, and phytomedicine (Naprisan®).

Disch et al reported the beneficial effect of iloprost in a man with sickle cell anemia and severe pain in both hips due to avascular necrosis. He was treated with intravenous iloprost (Ilomedin®), a stable analogue of prostacyclin (PGI₂) which causes arterial and venous dilation, stabilization of endothelial function, and inhibition of platelet and leukocyte activation. The patient experienced almost immediate pain relief and

remained pain free for at least 3 months, with mild headache the only side effect reported. Cordeiro and Oniyangi reported that Naprisan®, in a phase II study including 82 patients with SCD, was effective in reducing episodes of painful crises over a six-month period, with no serious side effects reported. Brousseau et al treated 19 children with sickle cell anemia or sickle-β⁰-thalassemia with intravenous magnesium sulfate, and found a significantly shorter length of stay in study admission compared to historical control.

The role of Naprisan® and magnesium sulfate in the management of painful crises is promising and further controlled studies are needed to confirm their salutary effect. If the effect of iloprost is sustained by larger studies, it would improve the quality of life of the increasing number of patients with SCD and avascular necrosis or other types of severe pain.

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Methods of Administration of Opioid Analgesics

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Established methods of administration of opioids have traditionally included the oral, intramuscular, intravenous, subcutaneous, transdermal, oral transmucosal, rectal transmucosal, nasal, epidural, and patient controlled analgesia routes. Recently reported novel methods of opioid administration to patients with SCD include:

- Transdermal iontophoresis using a patient-controlled delivery system. Delivery system was reported by Koo et al to deliver fentanyl to patients with pain other than SCD; this method appears ideal for patients with SCD with poor venous access;
- Nebulization to treat acute chest wall syndrome (Ballas et al)
- Implantable intrathecal drug delivery systems in patients with severe sickle cell pain (Smith et al, Ballas et al). The intrathecal dose is 1/100 that of the intravenous route and gives both local and systemic relief.
- Topical route to treat leg ulcer pain (Ballas). Here pain relief was achieved with lower doses than by the oral route. Of further interest, Peonawala et al showed that topical opioids heal ischemic wounds in the rat.

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Ballas SK. Treatment of painful sickle cell leg ulcers with topical opioids. Blood 2002; 99:1096.



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Poonawala T, Levay-Young BK, Hebbel RP, Gupta K. Opioids heal ischemic wounds in the rat. Wound Rep Reg 2005; 13:165-174.



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Adverse Effects of Opioids

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Administration of opioids to patients is known to be associated with side effects and with certain complications. Common side effects include pruritus, sedation, nausea/vomiting, constipation, and respiratory depression. Complications include addiction, physical dependence, tolerance, withdrawal, and pseudoaddiction. Opioid-related sedation can be severe and is usually associated with tiredness, fatigue, and respiratory depression that in many cases necessitates curtailing the dose of opioids needed to achieve pain relief. While the recent literature does not include large detailed studies on the frequency, severity, and outcome of the side effects/complications of opioids in patients with SCD, Elander et al, found that pseudoaddiction plays a more important role than genuine analgesic dependence in problematic pain management of patients with SCD. In addition, Ballas & Lusardi reported that about 5% of patients were readmitted to the hospital due to withdrawal, while Porter et al reported prolonged QTc interval (Torsade de Pointes) in an adult patient with SCD due to treatment with methadone for chronic pain.

In order to make a systematic assessment of maladaptive behaviors and examine their association with other factors, Elander et al conducted individual in-depth interviews with 51 hospitalized patients with SCD in London, UK, to apply preestablished criteria for concern-raising behaviors. These included disputes with staff, tampering with analgesic delivery systems, passing prescribed analgesics from one person to another, being suspected or accused of analgesic misuse, self-discharging from hospital, obtaining analgesic prescriptions from multiple sources, using illicit drugs, and injecting analgesics. Assessments were also made of pseudoaddiction, drug abuse, and pain coping strategies. The most frequent concern-raising behaviors were disputes with staff about pain or analgesics. Concern-raising behaviors were more closely associated with pseudoaddiction than with genuine substance abuse. The study by Ballas & Lusardi found withdrawal syndrome to be a cause for hospital readmission within one week after discharge, with sudden decrease in the daily dose of opioids upon discharge the likely culprit. Porter et al reported on an adult patient with SCD who developed Torsade de Pointes with ventricular tachycardia and prolonged QTc interval (454-522 msec). The patient was taking methadone 140mg q 6h (500mg/day) and no other causes of Torsade de Pointes could be identified.

More studies are needed to document the frequency and severity of the side effects and complications of opioids used in managing sickle cell pain. Adequate management of pain improves the quality of life of patients with SCD; achieving this goal entails understanding the behavioral factors and interpersonal dynamics that influence pain management. The study by Ballas & Lusardi suggests that the post-discharge period is a stressful situation that may precipitate a new painful crisis, and highlights the need for further studies to more specifically identify and manage these stressors appropriately. The letter to the editor by Porter et al is the first reported case of methadone-related Torsade de Pointes in a patient with SCD, a complication previously reported in patients taking methadone for the treatment of pain of other diseases (Krantz et al). This report suggests that patients with SCD who are taking methadone should have their EKG monitored and checked periodically. Finally, although there are no reports of its use in sickle cell patients, opioid sedation might be ameliorated by the use of small doses of psychostimulants such as methylphenidate, which have been reported useful in treating sedation in cancer patients.(Yee et al)

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Target Audience

This activity has been developed for Hematologists. There are no fees or prerequisites for this activity.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize the genetic, cellular, and environmental factors that can predict the frequency and severity of the acute sickle cell painful episode (crisis).
- Discuss the four distinct phases and associated hematological markers that describe the evolution of the sickle cell painful crisis.
- Outline current pharmacological approaches to managing sickle cell pain, including traditional and new drugs, methods of administration, and side effects.

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