

FAST FACTS AND CONCEPTS #270 PAIN IN SICKLE CELL DISEASE

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Background Sickle cell disease (SCD) is one of the most common genetic disorders in the world. It is recessively inherited and caused by a mutation in the hemoglobin β -globin chain gene (1). An estimated 90,000-100,000 people have SCD in North America; SCD occurs in 1 in 500 African-American births (2). This *Fast Fact* discusses issues specific to management of acute and chronic pain in SCD.

Mechanism of Disease Polymerization of deoxy-sickle hemoglobin injures the erythrocyte, leading to premature extravascular and intravascular hemolysis (1,3). Acute and chronic vascular endothelial changes facilitate adhesion of sickle erythrocytes and other blood cells, release of inflammatory mediators, vaso-occlusion, and end-organ damage, ultimately shortening the life span of affected individuals (3).

Disease Treatment Disease treatment involves preventive care and supportive therapies, including hydration, judicious use of blood transfusions, and prophylactic antibiotics. The only FDA-approved therapy for SCD, hydroxyurea, increases levels of fetal hemoglobin and total hemoglobin and reduces frequency of pain crises, blood transfusions, and acute chest syndrome (ACS) episodes (4). In select patients with severe disease, hematopoietic stem cell transplantation can be curative (5).

Pain and Vaso-occlusive Crises As fetal hemoglobin production diminishes around 6 months of age, painful vaso-occlusive crises (VOC) begin and recur with great variability in frequency and severity (6). Higher hematocrit, lower fetal hemoglobin, and presence of α -thalassemia trait are associated with increased rates of VOC. While many episodes have no clear trigger, common identifiable precipitants include dehydration, infections, psychological stress, menses, and weather changes. Recent data show one-third of patients having no VOCs for a year, and 17% having more than 3, with a 30-day re-hospitalization rate of 33% (7). Frequent VOCs are associated with early mortality, and can lead to chronic and intractable pain syndromes, greatly impacting sleep, mood, and social and physical functioning (8).

Management of the Acute Pain Crisis Successful pain management in VOCs depends on patient and clinician establishing trust, clearly defined expectations, and reasonable clinical goals (9). Negative provider attitudes towards acute pain in SCD, as well as misperception of pain behaviors as red flags for analgesic addiction, lead to under-treatment of pain (9). Clinicians more familiar with managing acute pain crises are more likely to believe patients' pain ratings (9).

- Pain crises last on average 9-11 days for hospitalized adults (4-5 days in pediatric populations) (10).
- The physical exam can reveal erythematous, swollen, and tender superficial bony areas (e.g., sternum, spine, ribs, wrists) but more often offers nonspecific findings (e.g. soft, tender abdomen). Although patients may have 'target' joints or areas of pain recurrence, they commonly report shift in locations of pain during a hospitalization.
- Management consists of supportive care with fluid hydration and aggressive pain control (1,11).
- Initiation and titration of opioid therapies remains a cornerstone for managing acute VOC pain (10,12). If IV access is challenging, parenteral opioids may be delivered subcutaneously. One small, randomized trial showed patient-controlled analgesia use was associated with similar analgesia but lower overall opioid use and side-effects compared to continuous infusion (13). Earlier retrospective studies linking morphine use to development of ACS have been refuted (14).
- VOC pain can be predictable enough to establish patient-specific pain protocols, which give dosing guidelines to clinicians such as emergency department staff who may be unfamiliar with the patient.
- Non-steroidal anti-inflammatory drugs (NSAIDs) may enhance relief and recovery (11), although large randomized controlled trials are lacking. There is no proven analgesic benefit to corticosteroids, neuropathic adjuvant agents, or red blood cell transfusions.
- While supplemental oxygen has no proven therapeutic role in patients with normal saturations, hypoxia in VOC may herald serious complications (e.g. ACS, stroke, pulmonary embolism). Incentive spirometry may prevent pulmonary complications leading to ACS (15).

- Low-dose intravenous naloxone infusion (0.25–2.4 µg/kg/hr) may relieve opioid-induced pruritis without affecting pain control. (16)

Chronic Pain in SCD

- Chronic pain in SCD is widespread and demonstrated to negatively impact functional status and QOL (17). Nearly 1/3 patients report pain on most days, and most pain exacerbations occur outside of health care settings (18). Although no evidence supports higher rates of opioid addiction in SCD patients compared with the general population, prescriber fears about addiction remain a barrier to adequate opioid administration (19).
- Chronic pain can develop from visible disease complications (leg ulcers, avascular necrosis) or a less well-understood transformation from persistent repeated VOCs into a chronic pain syndrome (13).
- Although specific guidelines are lacking, experts recommend an interdisciplinary approach to chronic pain management, and combining intervention modalities, including both pharmacologic (e.g. acetaminophen, NSAIDs, anticonvulsants, tricyclic antidepressants, opioids) and non-pharmacologic treatments (e.g. heat, massage, relaxation therapies, distraction, self-hypnosis, prayer/meditation, and acupuncture) (9,17).

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