

# PART II: PREVENTING AND MANAGING COMPLICATIONS OF SICKLE CELL DISEASE

## 1. PAIN

### Principles

- To educate patients, family and other caregivers about prevention, rapid identification and management of vaso-occlusive crisis.
- To manage sickle cell disease-related pain promptly and aggressively to reduce its impact on health-related quality of life.
- To treatment sickle cell pain optimally, using a combination of pharmacological, psychological and physical therapeutic approaches.
- To highlight the efficacy of hydroxyurea therapy in preventing or reducing the frequency of pain episodes in eligible patients.

No pain	Outpatient	Emergency	Inpatient	Post discharge
<ul style="list-style-type: none"> <li>•Prevention strategies <ul style="list-style-type: none"> <li>- Avoid extremes of ambient temperature</li> <li>- Hydration</li> <li>- Infection prevention</li> </ul> </li> <li>•HbF induction and WBC reduction <ul style="list-style-type: none"> <li>-hydroxyurea</li> </ul> </li> <li>•Chronic Transfusions</li> <li>•Education</li> <li>•Spleen exam by family</li> <li>•Surveillance for disease related complications</li> </ul>	<ul style="list-style-type: none"> <li>•Early, outpatients analgesics, targeted to severity of pain</li> <li>•Provide clear instructions</li> <li>•Provide support by phone</li> <li>•Consider non-pharmacologic interventions</li> <li>•Hydration</li> </ul>	<ul style="list-style-type: none"> <li>•Immediate initiation of treatment with regular intravenous or continuous opioids + NSAIDs/acetaminophen</li> <li>•Rehydration</li> </ul>	<ul style="list-style-type: none"> <li>•IV opioids (regular boluses or patient/nurse-controlled analgesia) <ul style="list-style-type: none"> <li>- Bolus doses for break-through. Short acting preferred</li> <li>- Frequent assessment and adjustment if necessary</li> </ul> </li> <li>•Non-opioid alternatives</li> <li>•Hydration.</li> <li>•Adjuvant support for potential analgesics' side effects (pruritus, constipation)</li> <li>•Close monitoring for serious side effects (hypoventilation, acute chest syndrome, seizure,). Treat as appropriate.</li> <li>• Incentive spirometry, encourage mobilization if possible.</li> <li>•Consider less common etiologies (osteomyelitis, avascular necrosis)</li> <li>•Provide multidisciplinary, social and family centered support</li> <li>•House staff education of patients treatment requirement</li> </ul>	<ul style="list-style-type: none"> <li>•Continue analgesics. Regular short acting preferred</li> <li>•Clear discharge instructions</li> <li>•Close follow-up</li> <li>•Adjust medications/doses as appropriate</li> <li>•Provide education, review strategies for future</li> <li>•Social support</li> <li>•Encourage activities, back to school</li> </ul>

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## Recommendations

### Education and Prevention

- Patients and caregivers should be educated about the triggers of vaso-occlusive episodes (VOE) and their impact on patients' health and quality of life. Triggers include dehydration, illness, fever, surgery, exposure to cold, and psychological stress.
- Clear instructions should be provided for the prevention of acute pain episodes – ideally at every clinic visit.
- The benefits of hydroxyurea for prevention of painful events should be reviewed with patients or their caregivers as early as possible, and on a regular basis. The potential side effects should be reviewed.
- The fear of triggering pain episodes should not limit patients' activities. If there are no other contraindications, patients with SCD should be encouraged to be as active as their peers.

### Home-based Management

- Patients or their caregivers should be provided with clear instructions for the identification of vaso-occlusive pain versus other potential and serious complications of SCD, including *acute chest syndrome* or *cholelithiasis*.
- Caregivers of young children with SCD should be familiar with examination of the spleen. Examination of the spleen is absolutely necessary to ensure that abdominal pain is not due to acute splenic sequestration. (*see Part II, section 8 on Splenic Sequestration*)

- Patients or their caregivers should be provided written instructions (and preferably in electronic format as well) for the management of sickle cell pain, including the type of medication, dosing options, and administration. This plan should be reviewed in each clinic visit, and modified if required.  
A clear instruction should be provided regarding when and how to seek help or to refer to emergency medicine.
- It should be ensured that patient has access to medication (over-the-counter or prescribed medications) when required. Medications that require a physician's prescription should be provided in advance, so that they can be used when necessary.
- Patients should be provided with the contact information of a health-care practitioner familiar with the management of sickle cell pain.

### **Outpatient Management**

- When adequate outpatient management is not sufficient to control the pain, the patient should be assessed in the sickle cell clinic/day hospital setting or in the ED if the clinic is unavailable.
- Patients should be assessed with priority upon arrival, and appropriate management should be started within 30 minutes. The initial treatment should be chosen to achieve appropriate pain control as soon as possible. Patients who have moderate to severe pain or those who were treated with oral opioids without successful pain relief at home should be given intravenous opioids after evaluation.
- The response to treatment and titration of medications should be frequently evaluated. An objective and age-appropriate method for grading the pain and the treatment response should be used.
- Patients should be started on hydration (preferably oral, if tolerated) to ensure that they are not dehydrated. Overhydration, however, should be avoided.
- If intravenous fluid is required, a hypotonic solution (such as 0.45% saline solution) is preferable over isotonic solutions, when there are no other concerns for hyponatremia.
- There is no proven benefit of oxygen therapy for a simple pain event, but it should be given if there is evidence of decreased oxygen saturation (<95%) or in the presence of respiratory symptoms.
- Depending upon the presenting symptoms, investigations may be considered, including complete blood count (CBC), reticulocyte count, cultures, bilirubin, liver enzymes, blood urea nitrogen and creatinine, blood gas, chest x-rays or other imaging studies. Risk of frequent radiation exposure should be kept in mind. For uncomplicated vaso-occlusive episodes, investigations may not be required.
- Patients should be evaluated for common etiologies of pain that may not be directly caused by SCD.
- For patients with abdominal pain, [examination of the spleen](#) is absolutely necessary to ensure that the pain is not due to acute splenic sequestration.
- Antibiotic therapy has no role in the management of a simple acute pain event, and when there is no fever or any other findings suggestive of infection. Physicians should be aware that patients with SCD may have a high baseline WBC count, and leukocytosis in isolation may not be due to infection. Nucleated red blood cells can also be erroneously counted as WBCs on automated CBCs – manual WBC count and WBC differential are often required.
- Red cell transfusions do not have a beneficial role in the management of acute painful episodes in SCD. The benefit of chronic transfusion therapy for the management of chronic sickle cell pain is controversial. ([see Part I, section 2 on Transfusion](#))
- Patients whose pain has been well controlled with oral medication, and who have been sufficiently observed and deemed safe for outpatient pain management may be considered for discharge, with sufficient education and a clear treatment plan for the next days. Physicians should ensure that each patient has access to the prescribed discharge medications in sufficient quantities.

### **Inpatient Management**

- Patients whose pain cannot be controlled by oral medications should be started on intravenous medications and be admitted to the hospital.

- Those with atypical pain or symptoms should be evaluated for an alternative etiology for the pain that may not be directly caused by SCD.
- Adjunct medications (e.g., non-steroidal anti-inflammatory medications [NSAIDs] and acetaminophen) should be used to reduce the rate of opioid infusion. These medications should be protocolized to optimize their use.
- Smaller doses of analgesics (around 50% of the maintenance dose) should be provided for breakthrough pain.
- Long-acting oral opiates should be considered for basal pain control if patients do not have a continuous IV opiate infusion.
- The response to treatment should be regularly evaluated, and analgesia dose should be reassessed on a regular schedule to titrate the medication dosing to optimize pain control.
- Step-down therapy should not be attempted until the pain is well controlled.
- For those patients whose pain is not controlled upon infusion of analgesics, a team that is expert in the management of pain (e.g., anesthesia, acute pain service) should be consulted, and PCA or NCA should be started.
- All patients, especially those with chest or back pain and those with supplemental oxygen requirement, should be started on age-appropriate incentive spirometry to prevent [acute chest syndrome](#).
- Fluid balance and hydration status should be monitored closely throughout the admission to avoid overhydration.
- The respiratory status of all patients on infusion of analgesics should be monitored. Other potential side effects of treatment (e.g., pruritus) should be addressed.
- Patients should be evaluated for constipation upon admission, and appropriate preventative measures should be provided.
- Provide non-pharmacological measures such as massage, heat pad, and distraction. Involve a pediatric life specialist for children. Encourage activities as tolerated.
- Once sufficient pain control is achieved, de-escalation of therapy can be attempted. Those whose pain is controlled on oral analgesics and deemed safe for discharge, can be sent home, but clear guidance for the management of pain and the possibility of readmission should be provided.
- Transfusion of packed red blood cells for the management of acute pain is not recommended. ([see Part I, section 2 on Transfusion for details on appropriate indications for transfusion](#))
- Patients should receive prophylaxis for venous thromboembolism, particularly if mobility is reduced during their hospitalization.

### **Choice of Analgesics**

- Patients should be treated with the most effective therapy with the least potential side effects for that individual patient. The response to treatment should be recorded in each patient's chart so it can be reviewed upon future admissions.
- Patients with adverse reactions to any analgesics should be provided with a written document indicating the type of adverse reaction, so that, in the future, an alternative treatment can be provided as soon as required.
- While on opioid analgesics, patients should also be treated with regular doses of NSAIDs (ibuprofen, naproxen, short-term Ketorolac) and acetaminophen as adjuncts to opioids to reduce the opioid requirement, unless their use is contraindicated.
- For breakthrough pain, short-acting medications are preferable over long-acting alternatives. Long-acting opioids are generally used for pain that is chronic in nature.
- Inhaled nitric oxide, corticosteroids, or magnesium sulfate have not been shown to be effective during acute painful events.

## Background

Pain is the most common presentation of sickle cell disease (SCD), and the most frequent cause of hospital admission, with major impact on patient quality of life.<sup>1,2</sup> It has been shown that frequent pain episodes are associated with early mortality in adults.<sup>3,4</sup> Although patients with sickle cell anemia (HbSS) and HbS-beta<sup>0</sup>-genotypes generally experience more painful episodes than those with hemoglobin SC disease (HbSC) or hemoglobin S beta<sup>+</sup>-thalassemia (HbSβ<sup>+</sup>), certain patients with HbSC or HbSβ<sup>+</sup> may have severe and frequent painful episodes requiring hospital admissions and aggressive pain management. Within each group of patients, the frequency and the degree of the pain are highly variable.<sup>5</sup> Due to the major impact of the pain on the health and quality of life of patients with SCD, inappropriate pain management may lead to suffering from suboptimal treatment or potentially life-threatening complications.<sup>6</sup>

The pathophysiology of pain in SCD is complex. The initial trigger is vaso-occlusion, with subsequent ischemia of tissues (commonly the bone marrow) and activation of inflammatory cascades, which will lead to inflammation and cytokine release.<sup>7,8</sup> Recurrent reactivation of pain fibers and associated neural networks leads to a hyperalgesic state, which causes amplified pain with each painful stimulus. In SCD, the complex interaction between red blood cells (RBC), white blood cells (WBC), platelets, and endothelium leads to activation of pain fibers, which leads to severe pain.<sup>7</sup>

It should be emphasized that, in addition to acute painful events, many patients with SCD also experience chronic pain. Under these circumstances, recurrent vaso-occlusive injury causes cumulative and chronic tissue insult and chronic inflammation. Physicians and health-care workers should be aware of the nature of chronic pain in these patients.

What defines the sickle cell pain is another challenging aspect of SCD care. Usually, patients are able to recognize vaso-occlusive pain. Other etiologies of pain that are common in patients with SCD, however, should be considered when dealing with a patient with acute or chronic pain (e.g., osteomyelitis, avascular necrosis of bones, cholelithiasis, constipation, acute chest syndrome, stroke, etc.). Note should be made that terminologies used to label a vaso-occlusive pain episode may vary by care provider and are generally interchangeable, including: vaso-occlusive episode (VOE), vaso-occlusive crisis (VOC), sickle pain episode and sickle cell crises.

## Management of Sickle Cell Pain at Home

Most patients with acute painful episodes will be treated at home, and do not require hospital visits or admission. It is therefore crucial to educate patients, families and caregivers of the signs related to sickle cell pain and its appropriate management at home.

Patients, families and caregivers should be educated about the “3 Ps” (or similar) approach to pain management, which incorporates physical, psychological and pharmacological strategies for pain management. In addition, communication with health-care practitioners familiar with the management of pain in these patients would be extremely helpful for providing appropriate guidance for optimal pain management and reduction of hospital admissions.

Non-pharmacologic interventions (e.g., heat packs and massage) as well as behavioral modification (e.g., coping mechanisms and distraction) should be considered as part of the management plan.<sup>9</sup>

## Management of Sickle Cell Pain in the Outpatient Setting

Patients should be seen in the day hospital/sickle cell clinic if they have inadequate pain control at home. If the clinic is not available, patients will need to be seen in the nearest emergency department (ED). Studies have shown that whenever available, day hospitals with trained personnel are superior to the ED for the management of uncomplicated painful events.<sup>10</sup> Once in their ED or day hospital, patients should be evaluated with priority and analgesic treatment should be initiated without delay.

In addition, patients should be started on oral or intravenous fluids to ensure adequate hydration or to provide necessary rehydration. This is usually achieved through more than maintenance fluid, but overhydration should be avoided, as it may lead to acute chest syndrome. Studies have suggested that fluids with lower sodium content may be beneficial, due to improved hydration of red cells and subsequent reduction in intracellular sickle hemoglobin (HbS) concentration.<sup>11</sup> Although no randomized trial has studied the ideal choice of fluid resuscitation,

when no other concerns for hyponatremia exist, it is reasonable to start patients on hypotonic saline solutions (most commonly 0.45% normal saline).

## Management of Sick Cell Pain in the Inpatient Setting

If appropriate pain control cannot be achieved by oral medications, the patient should be started on intravenous medications and be admitted to the hospital. The overall goal should be immediate control of the pain and early discharge, but this should not lead to the potential side effect of oversedation or risk of readmission. Pain-management approaches should follow a similar approach to the “analgesic ladder” for the treatment of cancer-related pain recommended by the World Health Organization. The choice and dosage of analgesic should be given according to the severity of pain in each individual patient.<sup>12, 13</sup>

The inpatient management of sickle cell pain can be challenging, and can lead to patient-caregiver conflicts. Variations in pain management may be caused by differing perceptions about the risk of opioid dependence, the suitability of opioids for SCD pain management, and the efficacy of parenteral opioid administration.<sup>14</sup> In general, patients with SCD may be opioid-tolerant, and therefore may require higher doses for the control of their pain.<sup>6</sup> Due to their higher dose requirements, these patients have an increased risk of opioid-related side effects, including respiratory depression and hyperalgesia. Health-care workers should be educated for this requirement, as suboptimal pain management may result in avoidable patient suffering. It is important to know that patients with SCD have not been shown to be at increased risk of opioid dependency compared with the general population.

In general, all opioids have common side effects that need to be carefully monitored and managed. Morphine, however, has been shown to be associated with an increased risk of acute chest syndrome.<sup>15</sup> Acute chest syndrome, a potentially fatal complication in patients with SCD, is more common in patients admitted for pain, likely due to overhydration, immobility, hypoventilation and/or opioid-induced vascular permeability.<sup>6</sup> Hence, all patients admitted with an acute painful event, and especially those with chest or back pain or patients with decreased O<sub>2</sub> saturation, should be started on incentive spirometry that is appropriate for the patient's age.<sup>16</sup>

If high doses of intravenous infusion of opioids along with adjunctive non-opioid medication and boluses for breakthrough pain are not sufficient to control the pain, then physicians who are specialized in the management of pain should be consulted. Patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA) has been shown to be a safe and effective alternative for the management of severe pain.<sup>16</sup>

## Choice of Analgesics

Recent evidence has demonstrated that the neurobiology of pain in SCD is more complicated than the simplified concept of ischemia-induced pain. In addition, subclinical studies as well as some clinical evidence indicated that current analgesics, including opioids, may exacerbate some underlying complications of SCD (renal disease, acute chest syndrome, seizures in those with history of stroke, hyperalgesia). Recently, great efforts have been made to investigate and develop new therapeutic options.<sup>17</sup> At the present, however, the mainstay of management of pain in SCD remains NSAIDs, acetaminophen, and opioid analgesics (e.g., morphine or morphine sulfate, hydromorphone; administered by either oral route, as intravenous single doses, or infusion – short acting or slow release). One thing that is certain is that the choice of analgesics should be carefully reviewed for each individual patient based on the past experience of patients and their SCD-related complications.

The recommendations for the dosing of medications for each specific scenario are beyond the scope of this consensus statement. It is encouraged that care centers develop a management guideline for administration of analgesics. Consultation with teams that have expertise in the management of pain should be sought, when the usual management is not sufficient to control the pain optimally or when there are contraindications for common analgesics.

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