



## **Sickle Cell Pain Outpatient and Crisis Guidelines**

## I. General Management: Outpatient

Pain management has traditionally been the focus of treatment for inpatients with sickle cell disease, but the assumption was that pain was infrequent in outpatients. Recently, pain in sickle cell disease has been proven to be the rule rather than the exception, occurring for most days in daily life for most sickle cell patients (Smith WR, et al, Ann Intern Med 2008). Further, recent NIH guidelines and an NIH consensus conference strongly endorse **hydroxyurea** for chronic sickle cell disease management, showing safe use as long as there is proper monitoring, and showing fewer crises and longer life. Last, hydroxyurea has been found beneficial even in children as young as 2 years of age. Thus, pain management in sickle cell disease will likely progress to more aggressive outpatient regimens.

The following are general recommendations that are included in patient education materials for treatment of individuals with sickle cell disease who are having a mild to moderate vaso-occlusive pain crisis. These guidelines are given to the patient by the health care team at the time of diagnosis and are continually and repeatedly reinforced over time.

- Rest, avoidance of overexertion.
- Oral Fluids: Intake should be at least 1-1½ times maintenance fluids for children or 128 oz of oral fluids for adults weighing 50 Kg. Fluids other than water are acceptable but not preferred. (Level of evidence: physiologic experiments in vitro, clinical experience)
- Analgesics: Ladder of short-term opioid use according to severity of pain (level of evidence: clinical experience, laboratory experiments, clinical trials in non-sickle cell patients)
  1. –Low severity: Acetaminophen and /or NSAIDs (Ibuprofen). Avoid more than 5 days of sequential Ibuprofen use, because of risk of ulcer and intestinal bleeding.
  2. –Moderate severity: Acetaminophen and /or NSAIDs (Ibuprofen) with moderate opioid (preferably oxycodone, which can be given without Tylenol)
  3. –High severity: Same as # 1 with stronger opioids (usually Morphine, Hydromorphone, or similar).
- Analgesics: Long-term opioids (Extended Release Morphine, OxyContin, Methadone, or Fentanyl Patches) for severe, chronic pain (more than 50% of days, more than 3 hospitalizations per year) Level of evidence: One before- after study in a major journal)
- Other Supportive Care Measures (Level of evidence: no evidence of effectiveness, but no harm from use)
  1. Warm compresses or heating pad; avoid cold exposure or ice applications
  2. Massage
  3. Relaxation Techniques/Hypnosis
- Signs and symptoms of need for emergency triage or urgent clinic visit
  1. Above management techniques are unsuccessful in providing relief over 24 to 48 hours

2. Pain worsens or is in unusual location (headache, left upper quadrant)
3. Weakness, especially in one part of the body
4. Priapism (painful erection of penis)
5. respiratory symptoms
6. Fever above 101<sup>o</sup> F
7. Signs of dehydration
8. Sudden change in vision, eye trauma (consult eye doctor immediately)

II. Hydroxyurea—the first anti-sickling agent approved by the FDA:

<http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines>

III. Emergency Outpatient Evaluation (Hematologist, Primary Care Physician, Emergency Department)

Evaluation should include the following:

- History
  1. Nature, location, duration and severity
  2. Precipitating factors
  3. History of analgesic use for this and previous episodes
  4. Accompanying symptoms: fever, shortness of breath, etc.
  5. History of previous serious sickle cell complications, e.g. acute chest syndrome, stroke, etc.
  6. Allergies
  7. History of cocaine use
- Physical Exam with special attention to areas at risk for sickle cell complications:
  1. Hydration status
  2. Cardio/Pulmonary exam
  3. Bone pain/swelling
  4. Sites of infection
  5. Abdominal (Liver and Spleen) /GU Exam (Priapism)
  6. Neurologic exam
  7. Pain Assessment

Diagnostics:

- CBC, platelet and reticulocyte count
- CXR with respiratory symptoms, O<sub>2</sub> requirement, or chest pain
- Blood culture if febrile; other cultures as indicated
- Consider renal and liver function tests if adult with no prior evaluation, or if on antibiotics or opioids
- Consider abdominal ultrasound, LFT's, amylase/lipase for RUQ, epigastric or severe abdominal pain.
- Type and cross match if Hgb is  $\geq 1.5$  gms. below baseline; request minor-antigen matched (if available), sickle negative, leukocyte depleted PRBC's.

## Therapeutics:

- IV Fluids: Initial rehydration with fluid of choice (Level of evidence: Physiological studies) Normal Saline, half Normal Saline, or similar. Rate, at 10-20 cc.'s/kg followed by 1-1½X's maintenance fluids with appropriate IV fluid.
- Antibiotics: As indicated (Level of evidence for output, for infection upon presentation: Randomized Controlled Trials)
  1. Outpatient: Pen V-K 125 mgs/250 mgs. PO BID (prophylaxis through age 6)
  2. Infection upon presentation: Ceftriaxone 50-75 mgs./kg./dose IV/IM (max. 2.0 gms./dose), or antibiotic to cover gram positive organisms
  3. If Penicillin allergic: Erythromycin (Clarithromycin, Biaxin, Zithromax, EES, etc.)
- Analgesic Choices for severe pain:
  - 1) Adults Outpatient:
    - a) Morphine (Immediate release) 0.2-0.5 mgs./kgs./dose PO Q2-4H prn pain
    - b) Hydromorphone 2-8 mg po q2-4H prn pain
    - c) Morphine (Sustained release) 0.3-0.6 mgs./kgs./dose Q8-12H (maintenance)
  - 2) Adults ED, Inpatient:
    - a) Ibuprofen 10 mgs./kgs./dose. PO Q6H (may alternate with acetaminophen; 200 mg tabs or 100 mgs./5 cc's)
    - b) Patient Controlled Analgesia: morphine or dilaudid. Titrate frequently to relief (Level of evidence, controlled trial in non-sickle cell pts)
    - c) Morphine 0.1-0.2 mgs./kgs./dose Q2-4H prn pain: Use scheduled dose, but patient may refuse. Titrate frequently to relief (Level of evidence: NIH Guideline 2002)
  - 3) Children, Inpatient:
    - a) Hydromorphone (dilaudid) 0.015 mg/kg/dose Q4H
    - b) Hydromorphone (dilaudid) 0.03-0.08 mg/kg/dose PO Q4-6H
- Analgesic Adjunct Medications and Treatments for Analgesic Side Effects:
  - 1) Benadryl 1.25 mg/kg/dose PO Q6H (max. 5 mg/kg/day) (25-50 mg for adults)
  - 2) Hydroxyzine 0.5 mg/kg/dose PO Q6H (max. 2.0 mg/kg/day) (25-50 mg for adults)
  - 3) Promethazine (phenergan) 0.25-0.5 mg/kg/dose (12.5-25 mg for adults)
- If there is little to no relief after 4-6 hours in the emergency department, admit to control pain.
- The patient who is discharged home should be treated aggressively with patient education aimed at instructing the patient that, if pain is chronic, taking both long acting opioids along with immediate release opioids will have the greatest chance of keeping the pain under control.
- Otherwise, for patients with infrequent pain, pain may be controlled with short-acting opioids for a defined period. Additionally, the use of regularly

scheduled anti-inflammatories can and should be used during resolution of the crisis.

#### IV. Inpatient Treatment Guidelines

##### 1) Pain Management

Practitioners should become familiar with the pharmacokinetics and relative potencies of opioid analgesics. While metabolism in individual patients may require titration when starting or changing opioids, an opioid conversion chart listing roughly equianalgesic doses of opioids is widely available in most hospitals, and should be consulted when making drug transitions.

If a patient is using a long-acting opioid (such as MS Contin, OxyContin, Methadone, or Fentanyl Patches) at home, this medication should be continued as an inpatient. When available, Patient-Controlled Analgesia (PCA) pumps should be used, per IV if access available, and per SQ if no IV access is available. IV drugs in order of choice are Morphine, Dilaudid, Fentanyl, and SQ drugs in order of choice are Morphine, Dilaudid, Fentanyl. Demerol is not preferred and potentially dangerous because of its toxic metabolite nor-meperidine, which predictably lowers the seizure threshold, rapidly accumulates in patients with renal insufficiency, and cannot be quickly measured.

Unless a patient has a documented life-threatening allergic reaction (i.e., difficulty breathing), then any of the above drugs are appropriate for use. Any side effects (i.e., nausea, vomiting, pruritus) can be controlled with the use of other appropriate medication.

There are occasional patients who require such high doses of opioid analgesics that it will be necessary to omit the long-acting opioid that they use as outpatients and use both a PCA dose and a basal infusion rate. Other sickle cell patients should not receive a basal rate because a continuous drug infusion rate may lead to life-threatening respiratory depression, especially in those who are opioid-naive.

The use of NSAIDs may be considered as an adjunct therapy in those patients whose BUN and creatinine are within normal limits and who have no history of acute or chronic renal failure. If NSAIDs are given, renal function must be monitored closely. Other measures (moist heat, massage, physical therapy, etc.) may be used as well.

Patients often use distraction mechanisms (i.e., talking on the telephone, walking in the hall, watching television, sleeping, etc.) in order to cope with pain. These coping mechanisms should *not* be misinterpreted by caregivers as indications that the painful episode has resolved and the patient may be discharged.

It is important to assess pain and to have an idea of the patient's relative pain intensity and response to treatment daily. One way to do this is by use of a

simple pain-rating scale (0-10). Note the location and intensity and whether or not it is a typical site and whether or not it feels like sickle cell pain. Monitor use of the PCA pump. Use in the past 24 hours can be reviewed on the pump display. The frequency of doses attempted and doses received (including boluses) as well as the patient's subjective report of pain may be used to titrate the opioid dose and make the patient comfortable, or to wean the patient in preparation for discharge.

When the PCA dose has been weaned adequately, convert to an equianalgesic oral medication using the opioid conversion chart. The patient should remain in the hospital for the next 2 -24 hours to ensure that the pain is controlled with adequate amount of oral opioids and/or NSAIDs and thus avoid the need for a possible re-admission to the hospital.

Upon discharge, if needed, the patient should be given a prescription for enough pain medication until the date of the next clinic appointment only. The patient should be scheduled for a follow-up visit and this date should be within 1-2 weeks after discharge from the hospital.

## 2) Hydration

Which fluids to use for maintenance hydration as an inpatient is somewhat controversial. Free water replacement vs. volume replacement are the guiding principles, and both are important, since patients cannot control the concentration of their urine output (renal medullary ischemia). One standard intravenous fluid recommendation is D5 1/2NS at 100-125cc/hour. Special care should be taken to avoid fluid overload in those patients who have chronic cardiac or renal disease. Ringer's Lactate should not be used as it may produce an acidotic state and therefore promote crises in sickle cell patients.

Oral hydration, though rare in the hospital, is acceptable for patients with poor venous access, using SQ opioids, and able to drink adequate amounts of fluids (1-2 liters/day). Patients must not be vomiting or nauseated and therefore unable to drink plenty of fluids.

Nurses should record I&O's daily. Patients should be observed for any sign or symptom of urinary retention (urine output <600cc/day, pelvic or abdominal distention/discomfort, etc.) as this may be a side effect of opioids. Patients should also be observed for any signs or symptoms of fluid overload (rales/crackles in lung fields, SOB, etc.) and have their IV fluids and oral intake adjusted accordingly and. Patients being fluid resuscitated may occasionally require a diuretic such as Lasix, especially after receiving blood.

## 3) Oxygen/Incentive Spirometry

Check pulse oximetry and if O2 saturation is 90% or more on room air, do not administer supplemental O2 as it may suppress the bone marrow's ability to manufacture new RBCs and thus prolong the crisis. If O2 saturation is <90% on room air, give humidified O2 at 2L/minute via nasal cannula and re-check the saturation level in 15 minutes to assure adequate oxygenation.

*Incentive spirometry*, (Level of evidence: Randomized controlled trial) improves both oxygenation and lung expansion, and prevents bone infarct-related acute chest syndrome. All patients with sickle cell pain should use the spirometer Q 2 hours while awake. Most patients will be on high doses of opioids, and at risk for respiratory suppression. Most will be lying in bed and at risk of atelectasis. It is especially important for patients with chest pain to utilize the spirometer as it decreases progression to Acute Chest Syndrome.

4) Bowel Regime

Because sickle cell inpatients usually receive high doses of opioids, constipation is a frequent problem. All patients on opioids should receive Pericolace or Senokot S BID. If patients report no bowel movement for 3 days, Milk of Magnesia (30cc/BID) and double doses of Pericolace should be added to the regimen. If they report no results by day 4-5, then add Dulcolax (tab or suppository/QHS). A Fleets enema or tap water enema may also be necessary.

Do not use Sorbitol as it can cause severe cramps and dehydration.

Instruct patients about foods (i.e, fiber, fruits, vegetables, etc.) and intake of fluids (especially water) that will aid in elimination.

5) Vital Signs/Height/Weight

Record patients' height and weight on admission. Weigh patients daily. Monitor vital signs at least once a shift. A physician should be notified by a nurse if temperature is 101.0 degrees or more, and because of sickle cell patients' high propensity for infection, urine and blood cultures must be done. Also, a physician should be notified if the apical heart rate is >100 or <60, if the systolic BP is >150 or <90, if the diastolic BP is >90 or <50, or if the respiratory rate is >24 or <12.

6) Nutrition

Patients can normally be fed a regular diet. A dietician can order extra snacks after (s)he knows patient=s preferences. Sickle cell patients generally need extra protein and calories to support their high metabolic rate, that is required to replace RBCs (the lifetime of sickled RBCs =10-20 days).

Patients may be allowed meal tickets if they are able to obtain their own meals or have someone (family member or friend - not one of the nurses) available to go to the cafeteria for them.

Nurses can obtain juice, ice, water, and a few snacks (soup, milk, ice cream, bread and sometimes a sandwich) from the kitchen galley on the unit.

7) Labs/Tests

Heme 18, a reticulocyte count, and a Basic Metabolic Panel should be obtained on admission, and repeated as clinically indicated. The Coulter counter WBC count may need to be corrected manually for nucleated RBCs found on the smear, which the machine counts as WBCs. Other tests should be ordered based on complications or symptoms.

8) Activity

Control pain as quickly as possible so that patients will be mobile. Patients should be up and ambulate and encouraged to ambulate. If patients are known or suspected users of illegal substances and have a PCA and/or IV, they should not be allowed off the unit without the removal of the PCA and/or IV line. Caregivers should initiate fall prevention guidelines as appropriate and accompany patients off the floor as needed.

If needed, order Physical Therapy and Occupational Therapy. Consider Physical Therapy for anyone not out of bed for 2-3 days.

9) Transfusions (Level of evidence: NIH Guideline)

The general indication for transfusion is to improve patients' O<sub>2</sub> carrying capacity.

Transfusion is mainly indicated for symptomatic anemia (signs of depletion of either oxygen or volume), often associated with a drop in Hb of over 1 gram. Always transfuse at least two (2) units of PRBCs. Excluding patients on transfusion programs for stroke prevention or other chronic reasons, acute prophylactic transfusions in patients without symptomatic anemia should be reserved for patients with Hb <4.5 grams (Level of evidence: clinical experience). Asymptomatic anemia with Hb  $\leq$  4.5 grams and an inappropriately low reticulocyte count may also be an indication for prophylactic transfusion, as it may indicate an aplastic crisis.

Do not transfuse simply for pain (Level of evidence: Clinical trials). Low-dose transfusion will not abort or prevent a crisis. Exchange transfusion may be indicated for acute chest syndrome.

Most patients will be able to tolerate an infusion rate of 1 unit of PRBCs over a period of 2 hours. A few will need to receive the infusion over a period of 3-4 hours in order to decrease the risk of fluid overload.

For surgery (non-minor), use simple transfusion to a pre-operative Hemoglobin of 10.0 grams. Transfusion for minor surgery may be optional in many patients.

10) Acute Chest Syndrome

Acute Chest Syndrome can be a life-threatening emergency. It is defined by chest symptoms (SOB, chest pain) and an abnormal chest x-ray (i.e., infiltrate). Other manifestations may include fever, hypoxia, and a decreased Hb level.

Patients with acute chest syndrome need to be monitored closely and may require intubation and/or transfer to the ICU.

Exchange transfusion is the preferred therapy for Acute Chest Syndrome in adults, whereas in children simple transfusion is more common. However, patients with a Hb <8.0 grams, cannot be exchanged safely. In these cases, simple transfusions to a Hb of 8.0 grams should be performed and then the patient should be re-assessed. If exchange transfusion is performed, a 16 gauge access or larger is required. Practically, this may mean insertion of a central line or a Quinton or Sorenson catheter.



### 11) Urine Tests for Opioid Use/Substance Abuse

Abuse of opioids is uncommon in sickle cell disease, but often suspected. Abuse of street drugs is more common than abuse of opioids, and rarely, diversion of opioids occurs. For known or suspected users of illegal substances, a urine drug screen must be obtained. Urine tests can identify recent use of both (prescribed) individual opioid medications and substances of abuse. Thus urine testing can be used to rule in appropriate use of opioids and rule out substances of abuse. The table below lists the length of time these drugs can be detected after use. These times apply to one-time use or following termination of dose use. Chronic use or abuse will extend the time these drugs can be detected in urine.

<b>Substance</b>	<b>Detection time</b>
Codeine	2-3 days
Dilaudid	2-3 days
Morphine (MSIR)	2-3 days
MS Contin	>2-3 days
Methadone (Quantitative)	2-3 days
Oxycodone (Oxy IR, Percocet, etc.)	1 day: difficult to detect unless specific search
Heroin	2-3 days, as morphine
Marijuana	2-3 days, recreational use; >20 days, chronic use

### 12) Individual Management Plans

Patients who are frequently in the ED and/or hospital may have an individualized care plan kept by their usual provider. These care plans usually include recommendations for pain management of the patient in the ED and hospital. They aid communication between providers who infrequently see patients and those who don't and eliminate mistrust of patients by physicians and vice versa.

**SAMPLE ADMISSION ORDERS – SICKLE CELL DISEASE**

DIAGNOSIS:  SS  SC  S-<sup>+</sup> THAL  S-<sup>0</sup> THAL  OTHER :

VOC  ACS  R/O SEPSIS  OTHER:

ADMIT:

ATTENDING PHYSICIAN

CONDITION:

DIET:

TPN: YES NO

ACTIVITY:

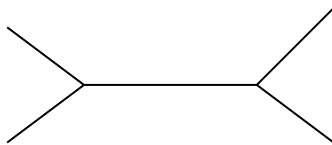
ALLERGIES:  NKA  Other:

VITAL SIGNS: Q4H WITH BP

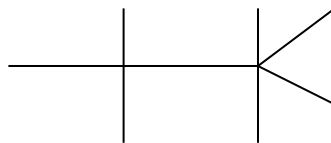
STRICT I and O **LABORATORY**

**TESTS :**

CBC  
Reticulocyte Count



Chemistries



Other:

**FLUIDS:**  PO intake > \_\_\_\_\_ cc/shift  
 IV: D5 \_\_\_\_\_ NS with \_\_\_\_\_ meq/KCl/L at  
 1500  2250  3000 cc/ \_\_\_\_\_ M<sup>2</sup>/day = \_\_\_\_\_ cc's/hr.

## MEDICATIONS:

Patient Controlled Analgesia (PCA) Orders

RN to check PCA pump Q 1 hr and document on Controlled Analgesia Log.

Access pain rating Q 2 hr while patient is awake.

Notify physician if pain uncontrolled for 2 hours.

Check sedation level Q 2 hr. Notify physician if patient is unarousable.

Check respiratory rate Q 2 hr. Discontinue PCA if respiratory rate is less than 12 per minute and notify physician immediately.

Check blood pressure Q 4 hr. Discontinue PCA if BP is less than \_\_\_\_/\_\_\_\_ and notify physician.

Notify physician if patient is unable to urinate.

Starting bolus before PCA is begun:

Morphine \_\_\_\_mg IV Q \_\_\_\_hr prn pain.

Discontinue once PCA pump is begun.

Drug:

Concentration: \_\_\_\_\_mg/ml

Interval Dose: \_\_\_\_\_mg = \_\_\_\_\_ml

Lockout Interval: \_\_\_\_\_minutes.

Basal Infusion Rate: \_\_\_\_\_mg/hr = \_\_\_\_\_ml/hr.

One Hour Dose Limit: \_\_\_\_\_mg/hr = \_\_\_\_\_ml/hr.

- ⑤ Acetaminophen 10-15mg/kg/dose x \_\_\_\_kg = \_\_\_\_mg PO Q6hr (max dose 4.gm/day)
- ⑤ Morphine 0.1 – 0.2 mgs/kgs/dose X \_\_\_\_kgs. = \_\_\_\_mgs ⑤ IV ⑤ IM ⑤ SQ Q2-4H prn pain.
- ⑤ Morphine (Immediate release) 0.2-0.5 mgs/kgs./dose X \_\_\_\_kgs = \_\_\_\_tabs PO Q2-4H prn pain. ( ⑤ 10 mgs/5cc ⑤ 20mgs/5 cc ⑤ 10 mgs tab ⑤ 20 mgs tab)
- ⑤ Morphine (Sustained release) 0.3-0.6 mgs/kgs/dose X \_\_\_\_kgs = \_\_\_\_tabs PO Q8-12H prn pain.( ⑤ 15 ⑤ 30 ⑤ 60 ⑤ 100 mg. tab)
- ⑤ Ibuprofen 10 mgs/kgs/dose X \_\_\_\_kgs = \_\_\_\_mgs PO Q6H (may alternate with acetaminophen;(200 mg tabs or 100 mgs/5 cc's)

**Adolescents (Adults):**

- 5 Hydromorphone (dilaudid) 1-4 mg/dose Q 4-6 hr 5 IM 5 IV 5 SQ 5 PO
- 5 Hydromorphone (dilaudid) 0.015 mg/kg/dose x \_\_\_\_\_ kg = \_\_\_\_\_ mg 5 IV  
5 SQ Q4-6 hr.
- 5 Hydromorphone (dilaudid) 0.03 – 0.08 mg/kg/dose x \_\_\_\_\_ kg = \_\_\_\_\_ mg PO Q4-6 hr.

**PRN Medications:**

- 5 Benadryl (Diphenhydramine) 1.25mg/kg/dose x \_\_\_\_\_ kg = \_\_\_\_\_ mg PO Q6H (max. 5mg/kg/day)
- 5 Atarax (Hydroxyzine) 0.5mg/kg/dose x \_\_\_\_\_ kg = \_\_\_\_\_ mg PO Q 6 hr (max 2.0mg/kg/day)
- 5 Promethazine (phenergan) 0.25-0.5 mg/kg/dose x \_\_\_\_\_ kg = \_\_\_\_\_ mg  PO  IM  
 IV  PR
- 5 Adult (max) 12.5-25mg Q 4-6 hr PRN

**ANTIBIOTICS:**

1. Pen V-K: 5 125mg 5 250mg PO BID.
2. 5 Ceftriaxone 50-75mg/kg/24 hrs. x \_\_\_\_\_ kg = \_\_\_\_\_ mgs. IM/IV  
Q12-24 hrs.(max. single dose: 2.0 gms)  
5 Cefuroxime 75-150 mg/kg/24 hrs. x \_\_\_\_\_ kg = \_\_\_\_\_ mgs  
IV Q8H (max. dose 6 gms./24 hrs.)
3. Other: Erythromycin as indicated, etc.

\_\_\_\_\_ MD/PNA

**References:**

[www.nhlbi.nih.gov/guidelines/scd/hydroxyurea\\_recommendations.pdf](http://www.nhlbi.nih.gov/guidelines/scd/hydroxyurea_recommendations.pdf)

Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, James AH, Laraque D, Mendez M, Montoya CJ, Pollock BH, Robinson L, Scholnik AP, Schori M. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med.* 2008 Jun 17;148(12):932-8. Epub 2008 May 5. PubMed PMID: 18458271.

Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, Rana S, Thornburg CD, Rogers ZR, Kalpatthi RV, Barredo JC, Brown RC, Sarnaik SA, Howard TH, Wynn LW, Kutlar A, Armstrong FD, Files BA, Goldsmith JC, Waclawiw MA, Huang X, Thompson BW, for the BABY HUG investigators. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG) *Lancet* 2011; 377: 1663–72

Smith WR, McClish DK, Penberthy LT, Bovbjerg VE, Dahman BA, Roberts JD, Aisiku IP, Levenson JL, Roseff SD. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med* 2008 Jan 15, 148(2):94-101.

Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med.* 1995 May 18;332(20):1317-22. PubMed PMID: 7715639.

Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, Orringer E, Bellevue R, Olivieri N, Eckman J, Varma M, Ramirez G, Adler B, Smith W, Carlos T, Ataga K, DeCastro L, Bigelow C, Sauntharajah Y, Telfer M, Vichinsky E, Claster S, Shurin S, Bridges K, Waclawiw M, Bonds D, Terrin M. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA.* 2003 Apr 2;289(13):1645-51. Erratum in: *JAMA.* 2003 Aug 13;290(6):756. PubMed PMID: 12672732.

Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W, Ataga K, Swerdlow P, Kutlar A, DeCastro L, Waclawiw MA; Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia and MSH Patients' Follow-Up. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. *Am J Hematol.* 2010 Jun;85(6):403-8. PubMed PMID: 20513116; PubMed Central PMCID: PMC2879711.

Payne R. Pain Management in sickle cell anemia. *Anes Clin North Amer* 1997; 15: 305-318.

Steinberg M. Management of sickle cell disease. *N Eng J Med* 1999; 340:1021-1030.

The management of sickle cell disease, National Institute of Health publications. No. 02-2117, Chapter 10. pages 59-74. Fourth Edition, revised June 2002.

Brookoff D, Polomano R. Treating sickle cell pain like cancer pain. *Ann Intern Med* 1992;116(5):364-368.