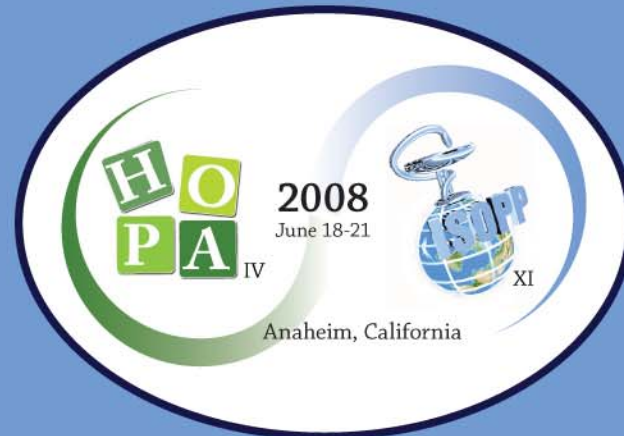


# Sickle Cell Disease

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# Disclosure

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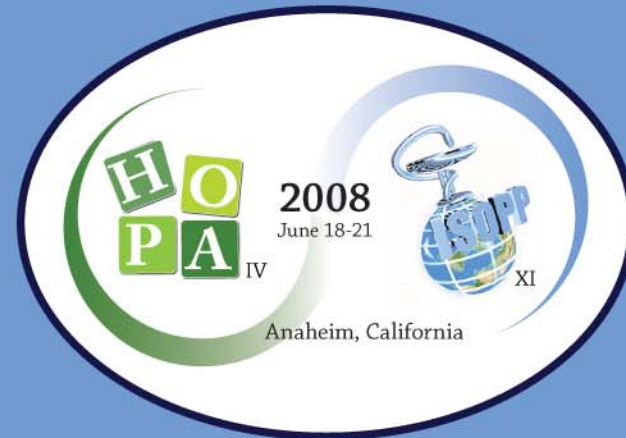
- Tracy M. Hagemann, PharmD has received consulting fees from LexiComp, Inc
- James Tjon, BSPhm, PharmD has no real or apparent conflicts of interest to report

# Learning Objectives

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- Review current principles and pharmacologic approaches to pain management in the sickle cell patient
- Apply principles of pain management to patient cases
- Describe the use of hydroxyurea in sickle cell patients
- Identify the desired therapeutic outcomes for patients treated with hydroxyurea
- Discuss future treatments for sickle cell disease (SCD)

# Sickle Cell Disease: Focus on Current Therapeutic Concepts



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# Opioids in Sickle Cell Disease

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- According to the American Pain Society (2002 Sickle Cell Management Guidelines), which is the most commonly used opioid in hospitals for sickle cell patients with acute painful episodes?
  1. Codeine
  2. Morphine
  3. Meperidine
  4. Hydromorphone
  5. Oxycodone

## ARTICLE

### Daily Assessment of Pain in Adults with Sickle Cell Disease

► Wally R. Smith, MD; Lynne T. Penberthy, MD, MPH; Viktor E. Bovbjerg, PhD, MPH; Donna K. McClish, PhD; John D. Roberts, MD; Bassam Dahman, MS; Imoigele P. Aisiku, MD, MSCR; James L. Levenson, MD; and Susan D. Roseff, MD

15 January 2008 | Volume 148 Issue 2 | Pages 94-101

**Background:** Researchers of sickle cell disease have traditionally used health care utilization as a proxy for pain and underlying vaso-occlusion. However, utilization does not completely reflect the amount of self-reported pain or acute, painful episodes (crises).

**Objective:** To examine the prevalence of self-reported pain and the relationship among pain, crises, and utilization in adults with sickle cell disease.

**Design:** Prospective cohort study.

**Setting:** Academic and community practices in Virginia.

**Patients:** 232 patients age 16 years or older with sickle cell disease.

**Measurements:** Patients completed a daily diary for up to 6 months, recording their maximum pain (on a scale of 0 to 9); whether they were in a crisis (crisis day); whether they used hospital, emergency, or unscheduled ambulatory care for pain on the previous day (utilization day). Summary measures included both simple proportions and adjusted probabilities (for repeated measures within patients) of pain days, crisis days, and utilization days, as well as mean pain intensity.

**Results:** Pain (with or without crisis or utilization of care) was reported on 54.5% of 31 017 analyzed patient-days (adjusted probability, 56%). Crises without utilization were reported on 12.7% of days and utilization on only 3.5% (unadjusted). In total, 29.3% of patients reported pain in greater than 95% of diary days, whereas only 5% reported pain in 5% or fewer diary days (adjusted). The frequency of home opiate use varied and independently predicted pain, crises, and utilization. Mean pain intensity on crisis days, noncrisis pain days, and total pain days increased as the percentage of pain days increased ( $P < 0.001$ ). Intensity was significantly higher on utilization days than on nonutilization days ( $P < 0.001$ ).

# Case Study #1

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- NM is 16 yo female with SCD (HbSS), admitted to ward with vaso-occlusive crisis (VOC)
- Chief complaint: 2 days acute pain bilaterally in legs and back, pain unresponsive to OTC prn meds, afebrile, Hb = 91 gm/L
- PMH: multiple admissions for VOC, 1 previous episode of acute chest crisis
- Medications: folic acid 5mg po qd, ibuprofen, acetaminophen prn
- Allergies: morphine – pruritus, ceftriaxone - hives & urticaria

# How Should NM's Pain Be Managed Optimally?

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# Sickle Cell Disease

- One of most common genetic diseases worldwide
- Abnormal hemoglobin predisposed to polymerization & consequent “sickled” RBCs
- Complications: hemolysis, vascular occlusion



RBC = red blood cells.

Stinson J, Naser, B. *Pediatr Drugs*. 2003;5:229-41.

# Pain in Sickle Cell Disease

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- Hallmark of SCD is *acute VOC*
- Severe SCD: occurrence of  $\geq 3$  crises
- Pain: multi-factorial complex human experience (eg, pathophys, psychol, social, cultural, etc)
- Frequent hospital admissions are known risk factor for early death in SCD
- Triggers: infection, temperature, stress, dehydration
- Physiologically is *nociceptive*: due to tissue damage (eg, interleukin-1, bradykinin, histamine, prostaglandins)

# Barriers to Pain Management

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- Clinicians' limited knowledge of SCD
  - Management of pain should be made within framework of disease
  - May be prodrome of serious complication
  - Incorrect attitudes and beliefs about opioids
- Inadequate assessment of pain
- Biases against opioid use
  - Opioid *tolerance* and *physical dependence*
  - Confusion with *addiction*

# Pain Syndromes in SCD

## Acute

- Most common
- Abrupt onset
- Days to weeks
- Recurrent episodes of pain, acute chest syndrome, priapism, splenic sequestration, cholecystitis

## Chronic

- Lasts  $\geq$  3-6 months
- No longer serves warning function
- Avascular necrosis, arthritis, leg ulcers, chronic osteomyelitis

## Neuropathic

- Uncommon
- Burning sensation, tingling, numbness
- Causes: nerve infarction, nociceptive substances, compression from bony structures

# Principles of Effective Pain Management

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- Thorough pain *assessment*
  - Should be done before and periodically
  - Relies heavily on patient self-report
  - Scales: visual analogue, faces, numerical, descriptive, multidimensional
- Utilization of non-pharmacological and pharmacological agents
- Comprehensive plan for disposition and longitudinal follow-up

# Non-pharmacological Management

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- Cutaneous stimulation (TENS, heat, cold)
- Relaxation
- Massage
- Music
- Self-hypnosis
- Acupuncture
- Heating pads
- Biofeedback
- Tub baths

# Pharmacological Management of Pain in SCD

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1. Non-opioids
  2. Opioids
  3. Adjuvants
- Major difference between non-opioids and opioids: *Ceiling Effect*

# Non-opioids

Drug Class	Max. Daily Dose (mg)	Half-life (hr)
Acetaminophen	4000	1-3
Non-selective COX-Inhibitors		
Acetylsalicylic acid (Aspirin)	4000	4-15
Ibuprofen (Motrin <sup>®</sup> , Advil <sup>®</sup> )	3200	2
Naproxen (Naprosyn <sup>®</sup> )	1500	13
Ketorolac (Toradol <sup>®</sup> )	120(IM/IV), 40(po)	3-8(IM/IV), 3-11(po)
Selective COX-II Inhibitors		
Celecoxib (Celebrex <sup>®</sup> )	400	11-12
Tramadol (Ultram <sup>®</sup> )	400	6

IM = intramuscular; IV = intravenous.

Ballas SK. *Hematol Oncol Clin North Am.* 2005;19:785-802.

# Classification of Opioids

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- Opioid agonists
  - Codeine, morphine, hydromorphone, hydrocodone, oxycodone, methadone, fentanyl, levorphanol, meperidine (diminished role in treating pain)
- Partial agonists
  - Buprenorphine
- Mixed agonists-antagonists
  - Pentazocine, nalbuphine
- Antagonists
  - Naloxone, naltrexone

# Considerations of Opioids

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- Factors in selection: type of pain, analgesic history, pain intensity, route of administration, provider comfort with analgesics, patient preference, cost, local availability
- Fewer systemic adverse effects than non-opioids, no ceiling dose
- Adverse effects: pruritus, sedation, respiratory depression, constipation, nausea & vomiting
  - Tolerance, adjunctive meds
- Seizures may be associated with certain opioids (eg, meperidine)
- Tolerance and physical dependence vs addiction

# Considerations of Opioids

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## ■ Pharmacokinetic

- Metabolism of codeine, hydrocodone, oxycodone, morphine
  - Most oral opioids undergo extensive liver metabolism
  - 5-10% of population cannot metabolize codeine
  - Morphine metabolized into M6G and M3G

## ■ Multiple routes of administration

- Continuous iv infusion, PCA, intermittent injection, oral (immediate release & sustained release)

## ■ Equianalgesic dosing

- Multiple methods: tables in pharmacy references, others take into account relative potency and pharmacokinetic parameters

PCA = patient-controlled analgesia.

Ballas SK. *Hematology Am Soc Hematol Educ Program*. 2007;97-105.

# Comparative Pharmacokinetics of Opioid Analgesics

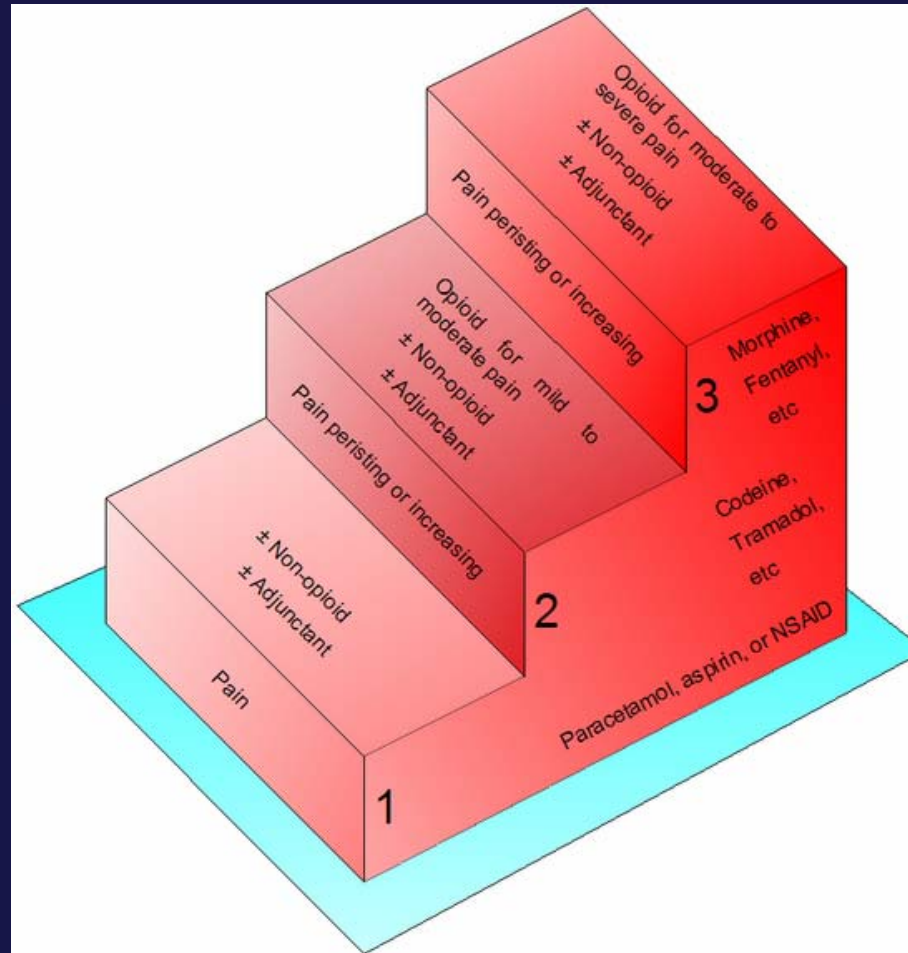
Opioid	PO Dose (mg)	IM/IV Dose (mg)	Duration of Action (hrs)	Plasma Half-Life (hrs)
Morphine	60	10	3-6	2-4
Codeine	200	120	4-6	3-4
Hydromorphone	7.5	1.5	4-6	2-4
Hydrocodone	5-10	n/a	4-8	3-4
Oxycodone	30	n/a	4-6	3-4
Meperidine	300	75	2-4	3-4
Fentanyl	n/a	0.1	1-2	1.5-6

# Adjuvants

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- Anti-depressants
  - Reduce pain perception, induce sleep, treat depression
- Benzodiazepines
  - Reduce anxiety, induce sleep
- Anticonvulsants
  - Stabilize neuronal membranes for analgesic effect
- Anti-histamines
  - Sedation, counteract histamine release by opioids

# WHO 3-Step Analgesic Ladder



# Cochrane Review

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- Objective: assess effectiveness of analgesics in children and adults with SCD
- Nine randomized controlled trials
  - NSAIDs (vs placebo & strong opioid), strong opioids (po vs iv, alternate), corticosteroids (vs placebo)
- Limitations of review
- Conclusions
  - No chronic pain, limited evidence in acute crises, benefit of SR po morphine, effect of corticosteroids, more research needed

# Guidelines for Management of VOC in SCD at Sickkids Hospital

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- Inpatient management
  - Treat with morphine as continuous iv infusion +/- morphine boluses
  - PCA considered for pain crisis lasting more than 24-48 hrs in pt >6 yrs or who has previously received PCA
  - Pts also receive IV fluids, stool softener, anti-histamine, incentive spirometry
  - Can step-down to acetaminophen with codeine or ibuprofen
- Outpatient management
  - Discharged home on acetaminophen with codeine or ibuprofen

# Back to NM...

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# Case Study #1

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- Started on hydromorphone PCA with hydromorphone po prn for breakthrough pain on April 10th
- Sedation secondary to hydromorphone, ketamine iv infusion added April 11th
- Developed fever during admission and started on clindamycin iv
- Discharged home on hydromorphone po prn April 16th

# Case Study #2

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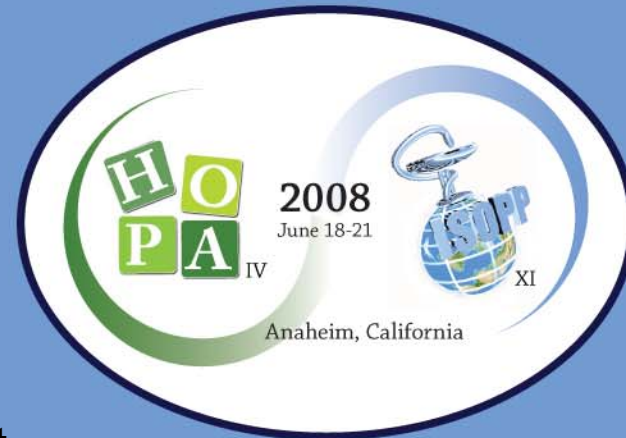
- JL is 9 yo male with SCD (HbSS), admitted to Pediatric Medicine ward from ER with VOC (3<sup>rd</sup> VOC in last 5 months)
- Home medications: penicillin, folic acid, codeine prn
- Started on morphine iv continuous infusion with morphine iv prn, achieving adequate pain relief
- What analgesic to discharge JL home on?

# Take Home Messages

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- Pain in SCD may be more prevalent and severe than previously demonstrated and may be misclassified and undertreated
- The use of a combination of treatment approaches and classes of drugs is more effective in achieving adequate pain relief
- Important to distinguish between physical dependence and tolerance with addiction

# Hydroxyurea in Sickle Cell Disease



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**Pediatric Hematology/Oncology Specialist**  
**University of Oklahoma Health Sciences Center**  
**Oklahoma City, Oklahoma**

# News Release – NIH

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- “Hydroxyurea treatment for sickle cell disease...does appear to be effective but [is] currently underutilized.”
  - ACS, March 14, 2008

# Case

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- PM is an 18-year-old patient with sickle cell disease (HbS)
  - Past medical history:
    - Cholecystectomy at age 15 years
    - Multiple admissions for VOC over past 5 years
    - Acute chest syndrome at age 8, 12, 15, and 16 years
  - Medications:
    - APAP/hydrocodone 7.5 mg PO q 4-6 hours PRN
    - Folic acid 1 mg PO daily
    - Ibuprofen 600 mg PO TID PRN pain

# Question

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- Is PM a candidate for hydroxyurea?

# Hydroxyurea

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- Ribonucleotide reductase inhibitor
- Approved by FDA in 1998 for treatment of SCD
  - ↑ HbF levels
  - ↑ HbF-containing reticulocytes and intracellular HbF
  - Antioxidant properties
  - ↓ Neutrophils and monocytes
  - ↑ Intracellular water content
  - ↓ Red cell adhesion to endothelium
  - ↑ Levels of nitric oxide

# Landmark Trial

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- Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia
  - Hydroxyurea vs placebo
  - 44% decrease in mean annual rate of pain crises
  - Also, fewer episodes of pain, acute chest syndrome, and PRBC transfusions
  - Study stopped early

# Additional Studies

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- Steinberg 2003 (9 year follow-up)
  - 40% reduction in mortality rates
    - Steinberg MH, et al. *JAMA*. 2003;289:1645-51.
- Belgian study, 1996
  - Ferster A, et al. *Blood*. 1996;88:1960-64.
- HUG-KIDS, 1999
  - Kinney T, et al. *Blood*. 1999;94:1550-54.
- Zimmerman, 2004
  - Zimmerman T, et al. *Blood*. 2004;103:2039-45.
- De Montalembert 2006
  - De Montalembert M, et al. *Haematologica*. 2006;91:125-8.

# Indications for Hydroxyurea

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- Adults, adolescents, children with SCD and:
  - Frequent pain episodes
  - History of acute chest syndrome
  - Severe vaso-occlusive events
  - Severe symptomatic anemia

# Question

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- Is PM a candidate for hydroxyurea?
- What initial laboratory work is required prior to treatment?

# Initial Laboratory Work

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- Blood counts
- Red cell indices
- % HbF
- Serum chemistry
- Pregnancy test
- Additional requirements
  - Willingness to follow treatment recommendations
  - Not participating in a chronic transfusion program

# Question

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- Is PM a candidate for hydroxyurea?
- What initial laboratory work is required prior to treatment?
- Identify treatment goals for PM

# Treatment Goals

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- Reduce the number and severity of pain crises
- Improve quality of life
- Decrease acute complications
- Increase in HbF to 15%–20%
- Avoid or monitor for adverse effects from hydroxyurea

# Adverse Effects

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- Myelosuppression
- Hyperuricemia
- NVDC, anorexia, pancreatitis
- Increased LFTs
- Rash, hyperpigmentation, pruritus
- Dysuria
- Long-term unknown: myelodysplasia, leukemia, opportunistic infection

# Question

---

- Is PM a candidate for hydroxyurea?
- What initial laboratory work is required prior to treatment?
- Identify treatment goals for PM
- What is the initial dose and how will you monitor for efficacy?

# Dosing

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- Initial 10–15 mg/kg/day once daily
- Increase by 5 mg/kg/day every 3 months to max of 35 mg/kg/day
  
- Adjust for renal impairment

# Availability

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- 200, 300, 400, and 500 mg capsules
- Extemporaneous compounding of liquid form
  
- Handle with precautions

# Efficacy Monitoring

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- Subjective
- Objective
  - Number of admissions for crises
  - HbF% every 6–8 weeks
  - CBC every 2 weeks initially
  - Chemistry panel every 2–4 weeks

CBC = complete blood count.

National Institutes of Health. The management of sickle cell disease. NIH Pub. No. 02-2117. Bethesda, MD: Division of Blood Diseases and Resources, Public Health Service, U.S. Department of Health and Human Services; 2002(Jun); 181. Available from: [www.nhlbi.nih.gov/health/prof/blood/sickle/sc\\_mngt.pdf](http://www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf). Accessed 6/2/2008.

# Monitoring

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- Mean corpuscular volume
  - If no increase with hydroxyurea use
    - Marrow not responding
    - Dose too low
    - Noncompliance

# Discontinue Therapy

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- Hb <5 g/dL
- ANC <2000/mm<sup>3</sup>
- Platelets <80,000/mm<sup>3</sup>
- Reticulocytes <80,000/mm<sup>3</sup> with Hb <9 g/dL
  
- Once recovered, restart with lower dose

ANC = absolute neutrophil count.

Sickle Cell Disease Care Consortium. Sickle cell disease in children and adolescents: diagnosis, guidelines for comprehensive care, and care paths and protocols for management of acute and chronic complications, November 2001. Available at: <http://www.scinfo.org/Protocol-2002.pdf>. Accessed 6/2/2008.

# Question

---

- Is PM a candidate for hydroxyurea?
- What initial laboratory work is required prior to treatment?
- Identify treatment goals for PM
- What is the initial dose and how will you monitor for efficacy?
- What patient counseling is needed?

# Patient Counseling

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- Avoid pregnancy – use 2 forms of contraception
  - Teratogenic
- Take on empty stomach at same time daily
- Notify health care provider if experience:
  - Sore throat
  - Bruising
  - Bleeding
  - Abdominal pain
  - Fever

# Patient Counseling

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- Take folic acid
  - Folate deficiency may be masked by hydroxyurea use

# Future Therapies

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- Fetal hemoglobin stimulators
- Transplant
- Others

# Fetal Hemoglobin Stimulators

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- Cytidine analogs
  - Decitabine
- Butyrates
  - Arginine butyrate

# Transplant

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- Bone marrow
- Stem cell
- Cord blood
- Partial chimerism

# Others

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- Niprisan
- Nitric oxide
- L-arginine
- L-glutamine
- Magnesium pidolate
- Zinc sulfate