Sickle Cell Disease - Update
Acute and Chronic Pain Management

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A lot of Pain

- 232 patients age 16 years or older with sickle cell disease – Diaries
- Pain reported 55% of days
- 13% at home pain crisis days
- 29% pts have pain 95% of days
Normal vs. Sickle red cells

If no oxygen, then pain and damage occurs
Clotting system is too active.

Fibrin clot blocks blood flow, then pain and damage occurs.
Sickle red cells are stickier.

Sticky red cells block blood flow, then pain and damage occurs.
Low levels of Nitric Oxide (NO)

Vasoconstriction blocks blood flow, then pain and damage occurs
SICKLE BIOCHEMISTRY

- Deoxygenation
- Intracellular hemoglobin concentration
- pH (Amount of Acid in the blood)
- Temperature
SICKLING - Hb CRYSTALS
Sickle Cell Disease
Complications

- Sickle cells become trapped and destroyed in the spleen causing Splenic Sequestration
- Anemia - hemolysis
- Pain episodes acute and chronic
- Gall Stones
- Strokes or aneurysms
- Kidney failure
- Pneumonia or Chest Syndrome
- Increased Infections
- Bone infarctions - AVN
- Retinopathy
- Priapism
- Iron Overload if transfused
ABC’s of Managing Acute Sickle Cell Pain

- **A** - Assessment of the pain
  - LOCATES, Typical pain?
- **B** – Believe the patient’s level of pain
- **C** – Complications or cause of pain
- **D** – Drugs and distraction
  - Pain Medication - WHO ladder
- **E** – Environment, rest in quiet
- **F** - Fluids – Hypotonic - D5W
  - Fixed dosing – NO PRN dosing
Acute or Chronic Pain

• Acute pain – hours to weeks
  – Sickle cell related or other cause
  – Treat the source and the pain level
  – Start with short acting analgesics progress to longer acting

• Chronic Pain – Over 6 months
  – Bone infarction, AVN…
  – Long acting safe NSAIDS
  – Long acting Opiates

• Both pain syndromes combined
  – Keep baseline treatment and add acute analgesics
Where is the Pain

- Atypical pain should prompt a search
- Head pain – Meningitis, Hemorrhage, Stroke, Infarction
- Chest Pain – Acute Chest, PE, Pneumonia
- Abdominal – RUQ gall stones, Hepatic sequestration, LUQ-splenic sequestration
- Back – Renal infarction, Salmonella Osteo
- Fever – sepsis, pyelo, osteo, pneumonia
- Multi-organ – Multi organ system failure
Work-up

- History – causes of increased sickling (dehydration, infection) – fever, N/V/D, headache, Abd pain, Chest pain, cough, urinary freq/urgency, dysuria, hematuria
- PE – Gen, HEENT, Chest, Abdomen, Extremity
- Lab- CBC/Retic, UA, Metabolic Profile
- Consider Type and cross if symptomatic or complication
- CXR if cough, dyspnea, pain. Bone films if focal bone pain and tenderness. CT for head and abdominal pain
Hand Foot Syndrome - Dactylitis

- Ages six months - two years. May be first presentation to ER
- This is treated with fluids and pain medication.
- Consider osteomyelitis
Abdominal Pain - Splenic Sequestration

- Sudden trapping of blood within the spleen
- May be associated with fever, pain, and respiratory symptoms.
- Circulatory collapse and death can occur in less than thirty minutes.
- Gall stones in children and teens - cholecystitis
Focal Bone Pain

Bone infarction, sickle arthritis, and aseptic necrosis of the femur or humerus.

Consider osteomyelitis if febrile or increased WBC.

X-ray, bone scan, MRI may help.
Fever indicates Sepsis until proven otherwise.

Do cultures then treat with antibiotics covering pneumococci.

Remember that the most common pain medications mask a fever (NSAIDS, acetaminophen).
MIXED PAIN SYNDROMES
Severe Acute and Chronic Pain
Pain + Weakness, Anemia, or Jaundice

Anemia – Hemolysis
Increased indirect bilirubin
Aplastic crisis from Parvo B16
Low retic count
Sequestration in the spleen or liver
high retic count
GI bleeding
Chest Pain - Acute Chest Syndrome

Chest pain
Infiltrate
Dyspna and Hypoxia
Treat with O², Transfusions and antibiotics
Prevent with incentive spirometry and pre-op transfusion to Hb 10
Headache – Strokes vs Meningitis

- Children have blocked flow
- Adults have aneurysms
- Presents with headache, weakness,
- Numbness, speech problems
- Fever or Increased WBC – Meningitis
- Trans Cranial Doppler (TCD) screening can identify kids at risk
- Transfusion for life or BMT
Lab Pearls

• Each patient has their own normal
  – Don’t treat the number - check the patient’s presentation
  – Usually Hct/Hb are low, WBC, Retics and Platelets are elevated
  – WBC >20K or left shift needs investigation
  – Indirect bilirubin and LDH are normally elevated with hemolysis
  – Direct bilirubin, Alk Phos, AST, ALT elevations should prompt Hepatic/GB work-up
  – LDH and high indirect bilirubin are normal in chronic hemolysis
Pain Assessment - VAS

- The Visual Analog Scale is a 10 cm line.
- The patient makes a mark from 0 = no pain to 10 = worst pain ever.
- A 10 cm ruler is used to determine the pain intensity.

Pain score is 6.5
WHO - Analgesic Ladder

1 (pain 1 – 3). Non-Opioid + Adjuvant

2 (pain 4 -6) Opioid for moderate pain + Non-Opioid + Adjuvant

3 (pain 7 – 10) Opioid for moderate to severe pain + Non Opioid + Adjuvant
Non-Pharmacological

- Relaxation - Biofeedback
- Distraction - Hobbies
- Massage
- Heating pad
- Quiet – calm environment
Pharmacological - Nonopioid

- Acetaminophen – safe if no liver disease, no GI or platelet effects- Adult dose 500mg – 1000mg every 4-6 hr. Do not exceed 3 gm/24 hours
  - Not Anti-inflammatory
  - Can add NSAID class like ibuprofen
  - Can add opioids
Pharmacological – Nonopioid NSAIDS

All are anti-inflammatory
- Aspirin
- Ibuprofen
- Naproxen - Naprosyn
- Sulindac - Clinoril
- Ketorolac - Toradol (IM/IV/PO)
- Salsalate - Disalcid
- Choline magnesium trisalicylate - Trilisate
- Bromfenac Sodium - Duract
- COX - 2 inhibitors – Celecoxib-Celebrex
Pharmacological - NSAIDS

• Cautions - Renal impairment, GI bleeding, Platelet dysfunction
• Omeprazole is gastroprotective
• Ceiling effect (do not push max dose)
• Can not add NSAIDs together
• Can add Opioids
Pharmacological – Nonopioid chronic / neuropathic pain

• Antidepressants
  – SSRIs
  – Duloxetine (Cymbalta) fibromyalgia/neuropathic

• Anticonvulsants - good for neuropathic pain
  – Pregabalin (Lyrica), Gabapentin (Neurontin)

• Anxiolytics – hydroxyzine (Vistaril)

• Antihistamines – diphenhydramine (Benadryl)
Tramadol

- Tramadol – (Ultram) Not DEA scheduled
- weak agonist at the mu opioid receptor
- inhibits reuptake of norepinephrine and serotonin, like a tricyclic antidepressant
- mild to moderate pain
- 25–100 mg oral every 4–8 hours Max 400 mg per day
- Can be addicting, No NSAID effects
- Not for those on antidepressants or seizures
Agonist - Antagonist Agents

- Usually have respiratory and analgesic ceiling. Good for acute pain episodes
- Nalbuthine (Nubain) 10 – 20 mg IM/IV q 3 hrs
- Butorphanol (Stadol) 1 mg Nasal, IM/IV
- Buprenorphine (Buprenex) 300 mcg IM or IV q6 hr - Used in opiate withdrawal and addiction treatment as Suboxone (combined with Naloxone) Patch for pain - Butrans
Pharmacological - Weak Opioid

- Codeine - Often combined with Acetaminophen as Tylenol #3
- Oxycodone - Percocet, Percodan, Oxycontin, Roxicodone
- Hydrocodone - Vicodin, Lortab
- DEA schedule III (http://www.usdoj.gov/dea/pubs/scheduling.html)
Pharmacological - Strong Opioids

- Morphine (MS-Contin, MSIR)
- Hydromorphone (Dilaudid)
- Meperidine (Demerol) **not first choice**
- Oxymorphone (Numorphan)
- Methadone (Dolophine) Long acting
- Fentanyl (Duragesic) Long acting
  - Transdermal Patch
  - Oral lollipop
  - Buccal quick acting (15 min)
- DEA schedule II

( http://www.usdoj.gov/dea/pubs/scheduling.html )
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<th>Analgesic</th>
<th>SC/IV/IM (mg)</th>
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<tr>
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<td>10</td>
</tr>
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<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>Oxycodone</td>
<td>-</td>
</tr>
<tr>
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<tr>
<td>10</td>
<td>Oxymorphone</td>
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Opioid - Considerations

- Safest Route - Oral, Rectal, Transdermal
- IV - PCA, or Fixed Dose
- NO PRN DOSING (except rescue doses)
- Use long acting with short acting for breakthrough pain
- No ceiling effect
- Spinal - Epidural and Intrathecal
- Prevent constipation
- Treat nausea, mental clouding, depression
- Rotate opiates to prevent tolerance
- Taper medication slowly - Decrease dose 15 - 20% daily and stop
Management of Severe Acute Pain NOT taking daily opiates

- Nalbuphine HCl 0.3 mg/kg up to 20 mg I.V. slow push q 3 to 4 hours. Total daily dose should be limited to 160 mg
- Add ketorolac 30 mg IV q 6 hours (NOT if renal disease or GI bleed history) Oral Ibuprofen 800mg PO q 8 hr is an alternative NSAID
- Adjuvants – Hydroxyzine for nausea or anxiety half dose q6 hr
- Consider adding acetaminophen q 6 hrs alternating with NSAID (if no hepatic dysfunction)
- IV D5W 250 cc/hr
Management of Severe Acute Pain taking daily opiates

- Morphine sulfate 0.05 to 0.08 mg/kg (3 to 5 mg) IV q 10 minutes until pain is controlled.
- Give the total dose required to control the pain q 3 hours IV. (Use PCA pump or IV push - NOT PRN)
- Add ketorolac 30 mg IV q 6 hours (NOT if renal disease or GI bleed history) Oral Ibuprofen 800mg PO q 8 hr is an alternative. Consider acetaminophen q 6 hrs
- Adjuvants – Hydroxyzine for nausea or anxiety half dose q 6 hr
- IV D5W 250 cc/hr
Who to Admit

• Pain that is not manageable at home after 8 hours of aggressive pain management
• Complications – Pneumonia, stroke, TIA, Chest syndrome, priapism, pregnancy, pyelo, osteo, multiorgan system failure, falling Hb/Hct, High WBC (20,000) Left shifts, fever…
Chronic Pain

• Maximize safest longest acting non-opioids
• Have fast acting opioid for breakthrough pain
• May need long acting opioid (methadone or long acting morphine)
• Consider a pain treatment contract and urine drug screening
• Rotate Opiates (prevent hyperanalgesia/tolerance)
• Add adjuvants – antidepression therapy
• Document well and have follow-up visits
Vocational Rehabilitation

- Job or hobby can be therapeutic
- Daily routine must not exacerbate pain
- Re-training may be required
- Social Workers and Vocational Rehabilitation counselors are great resources
Frequent pain events

• Worse disease, highest mortality
• Needs Case Management Plan
• Consider referral for **Hydroxurea** therapy
  – Reduces episodes by 50%
  – Reduces admits by 50%
  – Reduces need for blood by 50%
  – Prolongs life
Preventing pain - Hydroxyurea

- 1984 Hydroxyurea found to increase Fetal hemoglobin in sickle cell patients
- 1991 Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) stopped early 1995 because of benefits – reduced crisis, admits, transfusions all by 50%
- 2003 Hydrea prolongs life
- 2008 Consensus Statement from the NIH – Not used enough


Pain Prevention - FARMS

- **F** – Fluids, Folate, Fever, Fish
- **A** – Air, no smoking, no overexerting
- **R** – Rest, Relaxation
- **M** – Medications like Hydrea, Epo, Exjade, Penicillin
  - Medical care: Pain management, transfusions
  - Emergency care for weakness, chest, head, abdomen pain or fever
- **S** – Situations, Too hot or cold, Substances (no illegal drugs, alcohol, smoking)
  - Spiritual Life – If have one, you do better.
www.SCInfo.org

- World Wide Web Site - The Sickle Cell Information Center
  - http://www.SCInfo.org
  - Information for providers, patients, teachers, employers, administrators
  - Monthly E-mail Newsletter aplatt@emory.edu
  - Clinical guidelines as PDF files
Specific Problems: Pain Episode

Health Care Providers - Problem Oriented Clinical Guidelines

The most common acute problem and distressing manifestation in the patient with sickle cell disease is the sickle pain episode (also unfortunately termed pain “crisis”). A pain episode is defined as a self-limited episode of diffuse, reversible pain often occurring in the extremities, back, chest, and abdomen. The severity of pain has been reported to range from mild transient attacks of five minutes to excruciating pain lasting days or weeks requiring hospitalization. This intense pain is believed to be caused by the inflammatory response to bone or marrow necrosis, ischemic muscle, and ischemic bowel resulting from the obstruction and sludging of blood flow produced by sickled erythrocytes. The pain episode is almost never a cause of mortality, however, affected individuals often fear serious complications or death. The frequency of pain episode varies with each individual depending upon their hemoglobin phenotype, physical condition, and many other variables. Precipitating factors include alterations which cause increased physical and psychological stress, especially fever, dehydration, overexertion, rapid temperature change, or anger. Episodes, however, frequently occur without apparent antecedent causes.

by James Eckman, M.D. and Allan Platt, PA-C

Pain episodes are among the most troublesome and frequent complications of sickle cell syndromes. The patient develops severe pain in the extremities, back, and abdomen. A sickle pain episode is both uncomfortable and frightening to the patient, however, in itself almost never results in mortality. Pain episodes may be spontaneous or occur in association with physical or psychological stress. Treatment consists of resolving precipitating events, bed rest, hydration, and appropriate analgesics.

Clinical Findings

Subjective Data

Present Illness. Define the chief complaint, nature, location, severity, duration, and treatment of pain. Is distribution typical for patient’s pain episodes? Although pain in one location can be seen with pain episodes, localized pain may suggest a complication. Specific precipitating factors such as infection, dehydration, exercise, menstruation, or stress should be documented.

Review of Symptoms. Specifically exclude symptoms of infection such as fever, chills, cough, vomiting, diarrhea, dysuria, frequency, or headache.

Past Medical History. Document hemoglobin phenotype, general health, recent hospitalizations and surgery, allergies or sensitivities to NSAIDs or aspirin, usual treatment for pain episodes and previous response to therapy, and present medications.

Objective Data

Physical Examination
1 year ER visits in 637 Adults

Number of Visits - 1988

Visits per Year

- No Visits: 271
- 1 to 6: 237
- 6 to 12: 535
- 12 to 52: 433
- > 52: 1016
- > 52: 2767

Patients

Visits
Pain Crisis Episodes and Admissions per Active Adult

Pain Episodes per active adult

Case Management

1985 1987 1989 1991 1993 1995 1997 1999 2001 2003

3.1 Pain
0.5 Admit
Increases in Life Expectancy of Patients with Sickle Cell Anemia

All Americans

Hydrea

Sickle Cell Newborn Screening Program -PCN

Congress passes the National Sickle Cell Control Act

Sickle Cell Disease is Identified

Sickle Cell Anemia
PDA resources

- iPhone, iPad, iTouch – Pain Guide free
PDA resources

- iPhone, iPad, iTouch – Chronic Pain Tracker for patient diary- lite (free)
Books

- Hope and Destiny
- Overcoming Pain
- Renaissance of Sickle Cell Disease Research in the Genomic Era – Betty Pace MD
- See www.SCInfo.org
References Links

- http://www.ecu.edu/cs-dhs/medhum/newsletter/v1n2sicklecell.cfm
- http://sickle.bwh.harvard.edu/scd_history.html
- http://SCInfo.org