GUIDELINES FOR INPATIENT MANAGEMENT OF SEVERE VASO-OCCCLUSIVE PAIN EPISODES (VOE) IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

(Reviewed by Arpan Sinha, MD; Janna Journeycake MD; Amanda Linz MD; and Leigh Peek, Pharm D - March 2019)

Introduction: During vaso-occlusive pain episodes patients with sickle cell disease experience periods of severe pain which can last for several days. This treatment protocol will help with stabilization. (Refer to the ER pain algorithm for initial management).

Patient Eligibility: Patient with sickle cell disease in pain that did not respond to PO analgesics at home and has obtained short term or partial relief from parenteral analgesics in the ED or clinic setting. This protocol is designed for patients > 5 years old and without Significant Hepatic or Renal Disease. Recommendations for patients not fitting into these groups can be found under “special circumstances” at the end of this document. Patient allergies should also be taken into consideration when writing for these medications.

Treatment: Treatment of a vaso-occlusive episode includes hydration and analgesia and a multi-modal approach including non-pharmacologic treatment modalities.

A. Hydration:

Total fluids including the opioid infusion should not exceed 1 X maintenance unless evidence of dehydration. Avoid IV bolus unless patient appears dehydrated as this lowers the hemoglobin, often necessitating a pRBC transfusion which increases iron overload. Carefully monitor weight gain, edema, and pulmonary status. Do not use hypertonic fluids.

B. Analgesia

1. Non-Opioid Analgesics
   a. Non-Steroidal Anti-Inflammatories
      • Ketorolac 0.5mg/kg IV q6hr (30mg Max)
        o No more than 20 doses/month
      • If maxed on ketorolac: Ibuprofen 10 mg/kg q6hr PO (no more than 800mg/dose)
        o Start first dose on admission or 6 hr from last NSAID
      • All patients receiving NSAIDS should receive adequate GI protection with a H2 blocker/PPI. (Oral is preferred)
      • Make sure no increase in Creatinine prior to giving Ketorolac. Monitor Creatinine every other day while on Ketorolac.
   b. Centrally Acting Cox Inhibitor
      • Given parenterally for 24hrs and then converted to oral
        o Acetaminophen
          ▪ < 50kg then 15mg/kg q6hr IV
          ▪ ≥ 50kg then 1 gram q6hr IV
   c. Lidocaine Transdermal patch –
      • 12 hours on, 12 hours off.
   d. Other medications that maybe considered (Recommend starting one medication at a time to see effectiveness.)
      • Gabapentin: to be continued as an outpatient (If component of neuropathic pain)
• Baclofen prn: If presence of muscle spasm (should be used as a trial medication, if not effective then should not be continued)
• Melatonin 3mg qhs- for altered sleep habits in teenagers (This is a non-formulary medication at OU, so it requires an attending to order and approval by a clinical pharmacist).
• May consider initiation of SNRI like duloxetine for significant pain/anxiety/depression/altered sleep component only after performing a PHQ9 depression scale. (PHQ9 is important to screen for depression as well as to avoid masking of underlying depression with SNRI. It is available for download at https://www.uspreventiveservicestaskforce.org/Home/GetFileByID/218 SNRI should be started only after discussion with the sickle cell team and psychology input).

2. **Opioid Therapy**
The mainstay of therapy in these patients will be Patient Controlled Analgesia (PCA) for patients 5 years of age and older. This modality has been proven to increase patient satisfaction and decrease the nursing burden of providing intermittent bolus analgesics. Both a maintenance *basal* infusion will be utilized in addition to patient *demand* doses. Nursing boluses will be available for when the patient is maxing out their attempts and the nurse decides that the situation dictates an additional dose of medication Pro Re Nata (PRN). **RN should notify inpatient team if a patient needs more than 2 PRN doses in a 12 hour period.**

When the patient arrives to you they should have already received 3 doses of parenteral medication from the emergency department. Start with having the nurse administer the non-opioid analgesics and start your PCA (this takes time to acquire/set up). Morphine or Hydromorphone will be the opioids of choice. When starting a PCA please check what the patient has received during the previous admissions.

A few patients will arrive from the outpatient setting on long standing opioid regimens. These should be continued. If it takes a patient 60mg of oxycodone a day to be comfortable on a routine day, imagine what it would take to handle their pain on a day they present to the emergency room. **Long acting opioids in particular should be continued (Methadone, Morphine Sulfate ER, Oxycontin, etc.) Please consult pain service if patient is on a long-acting medication.**

<table>
<thead>
<tr>
<th><strong>RECOMMENDED STARTING DOSES OF MORPHINE</strong></th>
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<tbody>
<tr>
<td><strong>A.</strong></td>
</tr>
<tr>
<td>Initial loading bolus</td>
</tr>
<tr>
<td>Initial basal infusion (with PCA)</td>
</tr>
<tr>
<td>Intermittent PCA bolus</td>
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<tr>
<td>Nursing Bolus q1hr</td>
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<tr>
<td>Lockout</td>
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<tr>
<th><strong>RECOMMENDED STARTING DOSES OF HYDROMORPHONE</strong></th>
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</tr>
<tr>
<td>Initial loading bolus</td>
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<tr>
<td>Lockout</td>
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</table>
PLEASE DOUBLE CHECK YOUR MATH WITH A COLLEAGUE. A Decimal error can have serious consequences!!

Please do not start basal infusion if patient is obtunded after load. Ask nursing to wait until patient is interactive and with appropriate vital signs. (See monitoring Section on Page 4).

a. **Monitoring of opioid requirement**: Once a patient is started on a PCA; use the PCA monitoring flowsheet tool to document patient’s opioid requirement. Please remember that, nurses document in 12 hour shifts, so a common error is looking at 12 hr of PCA boluses instead of the 24hr total.

Ask patients and parents to evaluate pain on a 1-10 scale or on the Faces scale (for younger children). Please remember that a bolus takes 15 minutes to reach clinical effect with hydromorphone and with morphine peak effect occurs within 30 minutes from administration.

b. **Insufficient pain control** - If effective pain control is not achieved within 2 hours at the initial infusion rate, give an additional bolus of 0.05 mg/kg morphine or 0.01 mg/kg hydromorphone. **If patient requires > 2 rescue boluses in a 12-hour interval and patient is utilizing demand button appropriately, may increase the basal rate by 15-20%**. Subsequently can change lockout to: 8 minutes for morphine and 6 minutes for hydromorphone and encourage use of demand button. A lot of times, patients are not using the button effectively and must be encouraged to push.

c. **Discontinuing the infusion and transition to oral opioids** – Do not taper the opioid dose as soon as the patient becomes comfortable. This often results in a return of pain/anxiety. The infusion should be maintained for at least 36-48 hrs unless the patient is transitioned to an oral opioid equivalent.

    **Steps to transition:**
    If continuous (basal) rate is contributing to >50% of the patient’s total 24-hr opioid requirement, discontinue basal rate and continue demand only PCA. Based on the PCA requirement (demand doses) in about 24 hours time, calculate their total 24 hour demand and convert to oral opioid equivalent. If calculated oral opioid equivalent is not greater than weight- based dosing (for eg- not to exceed 0.02 mg/kg of oxycodone every 4 hours) convert to this oral dose. If patients have not required much and have been on the PCA for a very short amount of time (< 48 hours) – the conversion to oral medications can be done more quickly.

    **Criteria to be met to convert to Oral Medications**: (i) stable pain scores for 12-24 hours (ii) improving function as evidenced by ambulation, appropriate oral intake, etc. (iii) on a stable or decreasing opioid dose and (iv) calculated oral opioid equivalent is not greater than weight based dosing (for eg- not to exceed 0.02 mg of oxycodone every 4 hours)

d. **Patients that have frequent (> 6/year) and prolonged admissions (> 10 days) for pain**: PCA settings will likely be higher than usual recommended starting doses. Please refer to IV PCA settings from prior admissions and consult the Pain Management Service for assistance. Titration may be required initially to find a dose that provides relief without excessive sedation.

e. **Patients with hospitalizations for VOE >7 days**: Patients on high-dose opioids for > 7 days may require long-acting opioids for continued pain management
and/or prevention of withdrawal. Prescriptions should be for one week only and should be filled prior to discharge. Sickle cell pain action plan (In development) should be provided with times and doses clearly written out.

***SC team meeting (SC attending, team psychologist, SC NP, Pain Mgmt attending/PNP and SW) and assessment by staff psychiatrist for addiction/abuse potential and a signed contract will be necessary as determined by the SC team. This will be done if a decision is made to continue chronic opioid therapy.

### Equianalgesic Doses of Opioid Analgesics

<table>
<thead>
<tr>
<th>ORAL/RECTAL DOSE</th>
<th>ANALGESIC</th>
<th>PARENTERAL (IV) DOSE (MG)</th>
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<tbody>
<tr>
<td>30</td>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td>7.5-8</td>
<td>Hydromorphone (Dilaudid)</td>
<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>Oxycodone</td>
<td>(not available)</td>
</tr>
<tr>
<td>see below</td>
<td>Methadone*</td>
<td>see below</td>
</tr>
<tr>
<td>(not available)</td>
<td>Fentanyl*</td>
<td>0.1 (100mcg)</td>
</tr>
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- *Methadone and fentanyl are complicated medications, only to be prescribed after consultation with the sickle cell team and pain service/ Dr. Amanda Linz
- Codeine and combination medications such as hydrocodone-acetaminophen is not recommended and should be avoided.

### MULTIMODAL APPROACH: FOR ALL PATIENTS

**Behavioral coping strategies, including implementation of diaphragmatic breathing, use of distraction, relaxation skills, and cognitive coping strategies are recommended to incorporate into long-term treatment.**

**Consider consultation with our social work (Javey Dallas, MSW, LCSW) or psychology (Sunnye Mayes, Ph.D. or Carrick Carter, Psy.D.) team for intervention as needed.**

**Therapy dogs, art therapy, music therapy, video games, and child life involvement are strongly recommended as resources permit. These activities are particularly helpful for implementing the behavioral pain management strategies.**

### Monitoring of the Patient

1. Daily weights. Strict input and output.

2. Always place a pulse oximeter while the patient is receiving morphine or hydromorphone by continuous infusion. This may be removed temporarily if the patient is up walking.
3. Vital signs should be obtained frequently because of the possibility of respiratory depression. They should be taken at the beginning of the infusion with a recheck of pulse and respirations Q 30 minutes x 2, and then Q 2 hours x 2. If vital signs are stable at this point, they can be done Q 4 hours. If the dose is increased, pulse, respirations, oxygen saturations should be checked in 1 hour and rechecked Q 2 hours x 2. BP should be checked at least Q 4 hours and the patient should also be checked Q 4 hours for arousability. Leave clear orders as to acceptable limits for blood pressure, pulse, respiratory rate and oximeter readings. Standard orders are available.

4. CBC and reticulocyte count should be performed on admission, after 24 hours and then every other day.

5. CMP (comprehensive metabolic panel) and LDH should be performed on every patient on admission with a BMP (basic metabolic panel) every other day thereafter.

6. The level of pain may vary greatly from hour to hour. Ask the patient or parent about the level of pain and degree of pain relief using pain assessment scales appropriate for age (1-10 scale for older children and “Faces” scale for younger children). Increase or decrease the infusion rate as needed for relief of pain or to diminish side effects. Assess the patient's degree of discomfort before and after each dose change and evaluate for side effects. (If a patient has chronic pain, frequent checks may be counter-productive. May need to have an order to assess once a shift once stable).

Management of Side Effects of Opioids

1. Respiratory Depression: - Should the patient become difficult to arouse or should the respiratory rate fall below the set limit (10 per minute in an adolescent; 16-20 per minute in a younger child), or should the 
\[O_2\] saturation consistently fall below 90% when awake, the infusion should be stopped temporarily until the patient returns to a normal respiratory rate and is responsive to questions. The infusion should be restarted at that point at half the previous rate and titrated carefully.

In the case of severe respiratory depression or overdose, the infusion should be stopped and the patient given Narcan (naloxone) 0.01 mg/kg IV or IM. This dose may be repeated every 2 or 3 minutes x 2 doses. If that dose is ineffective, the dose should be doubled and repeated x 2. Narcan will rarely be needed but should always be readily available when a patient is receiving opioids by continuous infusion. Remember that administration of Narcan will reverse the pain relieving effect of the opioid!

2. Prevention of Acute Chest Syndrome: - Occasionally patients with sickle cell disease will develop acute chest syndrome while being treated for vasoocclusive crises. WE RECOMMEND INCENTIVE SPIROMETRY Q 2 HOURS EXCEPT BETWEEN 2200 AND 0700 FOR EVERY PATIENT ON A CONTINUOUS OPIOID INFUSION.

Any patient who develops respiratory distress or fever or who has experienced a period of respiratory depression needs to be evaluated by CXR. If pulmonary infiltrates are seen on CXR it may be necessary to change management in accordance with the acute chest syndrome guidelines.

3. Nausea and Vomiting: - If this becomes a problem, treat with antiemetics, e.g.
Ondansetron or Promethazine. Promethazine should not be used in children < 2 years of age due to the risk of respiratory depression (Black Box warning per FDA). Nausea and vomiting are typically transient side effects when due to opioid administration.

4. **Constipation**: Patients should be started on a stimulant laxative and an osmotic laxative. (See table below for appropriate laxative options and doses.) Miralax alone is often insufficient. Monitor for constipation and increase bowel regimen if constipation develops. Constipation is the only opioid-induced side effect that does NOT go away with time!!

<table>
<thead>
<tr>
<th>Stimulant Laxatives</th>
<th>Osmotic Laxatives</th>
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<tbody>
<tr>
<td>Sennosides (Senna)</td>
<td>Lactulose</td>
</tr>
<tr>
<td>12mo-6y: 2.5-5mg/day</td>
<td>1-2 g/kg, once or</td>
</tr>
<tr>
<td>6-12y: 7.5-10mg/d</td>
<td>twice/d</td>
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<tr>
<td>&gt;12y: 15-20mg/d</td>
<td></td>
</tr>
<tr>
<td>Bisacodyl (Dulcolax)</td>
<td>Polyethylene glycol (Miralax)</td>
</tr>
<tr>
<td>3-10y: 5mg/d</td>
<td>0.2-0.8g/kg/d</td>
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<tr>
<td>&gt;10y: 5-10mg/d</td>
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*www.nasphgan.org* (Peds GI Recommendations)

5. **Pruritus**: A low-dose naloxone drip may also be used at 1 mcg/kg/hr and titrated to effect (max dose 2 mcg/kg/hr). Patients should not be classified as allergic to morphine or to hydromorphone on the basis of itching alone.

Diphenhydramine and hydroxyzine - Use **oral formulation only**. May add PRN as well. For questions or problems, please contact the Pediatric Heme/Onc fellow/attending on call. For questions about dosing contact Clinical Pharmacy Services.

**SPECIAL CIRCUMSTANCES**

**Guidelines Modifications for Patients with Hepatic Disease:**

1. The above protocol minus the use of the following:
   a. Ketorolac: Only excluded in the setting of end stage liver disease (with documented INR escalation)

**Guideline Modifications for Patients with Renal Disease:**

1. The above protocol minus the use of the following:
   a. Ketorolac: Due to Concerns with Nephrotoxicity
   b. Start basal infusion at half calculated rate.
   c. Consider fentanyl as the opioid of choice with significant renal disease affecting clearance of opioids (Remember that it is quickly cleared initially but will have more prolonged effects at higher doses and after longer administration time. Recommend consultation from the pain team/Dr. Linz if fentanyl is needed as dosing is different)

**Guidelines for Patients Under the Age of 5**

1. Do not follow the above protocol for PCA
2. Resume Home Oral Opioids
3. Ketorolac 0.5mg/kg to max 30 mg every 6 hrs should be initiated
4. Morphine 0.1mg/kg q4hr IV PRN
WHEN TO CONSULT PAIN TEAM:

- Unable to wean opioid PCA by day 4 of hospitalization (opioid requirements keep increasing)
- Patient who is on long acting opioids at home (chronic opioid therapy for e.g. methadone or morphine ER, oxycontin etc) consult at admission
- Complicated VOC - with severe ACS (for e.g worsening hypoxia with sedation)
- Severe adverse reactions to opioids
- Difficulty managing pain (Call at any point)
- Readmission for management of vaso-occlusive episode within 7 days of prior discharge.
- Patient with renal disease requiring conversion to fentanyl or initiation of fentanyl for other reasons