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Objective:

To critically review the guidelines on vaso-occlusive complications and acute chest syndrome for sickle cell disease

Common triggers include stress, exposure to cold, and infectious illnesses.

Patient-controlled analgesia (PCA): A method of safely administering intravenous opioids which is controlled by the patient.

Mild Pain: Noticeable but tolerable, does not interfere with sleep or activities (able to cough, deep breath and ambulate)

Moderate Pain: Strong, deep, distressing, interferes with sleep and activities (coughing, deep breathing, ambulation)

Severe Pain: Very intense, dominates thought, prevents sleep and movement

Inclusion Criteria:

-All patients with sickle cell disease

Exclusion Criteria:

-None

Definitions:

Vaso-occlusive complications (VOC) crisis: A VOC manifests as acute excruciating pain, most commonly in the extremities, chest, and back. Onset is typically sudden sometimes gradual. Duration may be from hours to days.



Target Guideline Users:

All clinicians caring for pediatric and adult patients presenting with vaso-occlusive complication and acute chest syndrome with sickle cell disease within OHSU

Guideline Review:

1. How many patients with sickle cell disease died from opioid pain reliever overdose?
2. For adults and children with Sickle Cell Disease-related acute pain, what are the most effective pain management strategies?
3. In people with SCD and acute chest syndrome (ACS), what is the most effective treatment to reduce mortality, resolve pain, and prevent clinical deterioration?

Quality Measures:

Process:

- Time to first opioid
- Time to bed
- Time to pain relief
- Time to analgesia
- Time to fluids (IV)
- Pain Scores
- Sedation Scores

Outcome:

- Development of Acute Chest Syndrome
- Length of stay
- Readmissions
- Patient Satisfaction



Sickle Cell Disease
Existing External Guidelines/Pathways/Order Sets

Existing External Guidelines

External Guideline	Organization and Author	Last Update
Virginia’s Sickle Cell Disease Pain Crisis Guideline	Virginia Premier Health Plan	2016
Management of Sickle Cell Disease: Recommendations from the 2014 Expert Panel Report	American Academy of Family Physicians	2015
Evidence-Based Management of Sickle Cell Disease	National Institutes of Health: National Heart, Lung, and Blood Institute (NHLBI)	2014
Sickle cell disease: managing acute painful episodes in hospital	National Institute for Health and Care Excellence (NICE)	2012
Sickle Cell Disease – Critical Elements of Care	Seattle Children’s Hospital	2012
Sickle Cell Disease in Childhood: Part II. Diagnosis and Treatment of Major Complications and Recent Advances in Treatment	American Academy of Family Physicians	2000

The ten published clinical guidelines were evaluated for this review using the **University of Pennsylvania’s Center for Evidence-Based Practice Trustworthy Guideline rating scale**. The scale is based on the Institute of Medicine’s “Standards for Developing Trustworthy Clinical Practice Guidelines” (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.



Guideline Issuer and Date	VPHP 2016	AAFP 2015	NHLBI 2014	NICE 2012	SCH 2012	AAFP 2000
1. Transparency	C	B	A	A	B	B
2. Conflict of interest	C	C	A	NR	NR	C
3. Development group	C	B	A	A	B	B
4. Systematic Review	B	A	A	B	B	B
5. Supporting evidence	B	A	A	A	C	
6. Recommendations	A	A	A	B	B	B
7. External Review	C	C	A	NR	NR	C
8. Currency and updates	B	B	B	B	B	C

See appendix B for full description of the Trustworthy Guideline grading system.



			<p>Consensus–Panel Expertise</p> <ul style="list-style-type: none">- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with SCD presenting with fever or worsening anemia).- Recommendations were based on the panel’s expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain). <p>Consensus–Adapted</p> <ul style="list-style-type: none">- These recommendations were based on the panel’s expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD). <p>The panel clearly identified these statements as consensus recommendations and</p>			
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			acknowledges that these areas represent gaps in the evidence base and areas for future research.			
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Evaluating the Quality of Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. For more detailed information, see Appendix A.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Question 1: How many patients with sickle cell disease died from opioid pain reliever overdose?

In 2016, the **American Academy of Pain Medicine** released a report by Ruta and Ballas using the Centers for Disease Control and Prevention (CDC) database to determine how many patients with sickle cell disease died from opioid pain reliever overdose.



Table 1 Comparing number of deaths due to opioid pain relievers of non-sickle cell disease patients with the number of deaths due to opioid pain relievers of sickle cell disease patients from 1999 to 2013 in the United States

Year	Non-SCD Patients Who Died Due to OPR	SCD Patients Who Died Due to OPR
1999	4,022	8
2000	4,393	7
2001	5,521	7
2002	7,450	6
2003	8,513	4
2004	9,856	1
2005	10,922	6
2006	13,717	6
2007	14,401	7
2008	14,795	5
2009	15,594	3
2010	16,641	10
2011	16,907	10
2012	16,002	5
2013	16,225	10
Totals	174,959	95

OPR = Opioid Pain Reliever; SCD = Sickle Cell Disease.
Reference: Multiple Cause of Death Data, 1999-2013. CDC WONDER Online Database. 2015. Available at <http://wonder.cdc.gov/mcd.html>.



Table 2 Total number of deaths due to opioid pain relievers in different non-cancer disorders from 1999 – 2013 in the United States

Cause of Death	Total Number of Deaths Due to All Causes	Death Due to OPR	Percentage
Heart Disease	20,595,492	21,656	0.11
Fibromyalgia	3,282	144	4.4
Low Back Pain	3,758	80	2.1
Migraine	2,286	103	4.5
Sickle Cell Disease	12,261	95	0.77

OPR = Opioid Pain Relievers.

Reference: Multiple Cause of Death Data, 1999-2013. CDC WONDER Online Database. 2015. Available at <http://wonder.cdc.gov/mcd.html>.

References:

1. Ruta, N. S. and S. K. Ballas (2016). "The Opioid Drug Epidemic and Sickle Cell Disease: Guilt by Association." Pain Medicine 17(10): 1793-1798.

Question 2: For adults and children with Sickle Cell Disease (SCD)-related acute pain, what are the most effective pain management strategies?

Guideline Recommendations:

The **2014 National Heart, Lung, and Blood Institute (NHLBI)** expert panel report recommended the following for managing pain in patients with sickle cell disease and a vaso-occlusive crisis:

1. In adults and children with SCD and pain,
 - When indicated, initiate diagnostic evaluation of causes of pain other than a Vaso-Occlusive Crisis (VOC) while beginning to treat pain. **(Consensus-Adapted)**
2. In adults and children with SCD and a VOC
 - Determine characteristics, associated with symptoms, location, and intensity of pain based on patient self-reported and observation. If the VOC pain is atypical, investigate other possible etiologies of pain. **(Consensus-Adapted)**
 - Rapidly assess the patient’s recent analgesic use (opioid and nonopioid). **(Consensus-Adapted)**
 - Rapidly initiate analgesic therapy within 30 minutes of triage or within 60 minutes of registration. **(Consensus-Panel Expertise)**
 - Base analgesic selection of pain assessment, associated symptoms, outpatient analgesic use, patient knowledge of effective agents and doses, and past experience with side effects. **(Consensus-Adapted)**



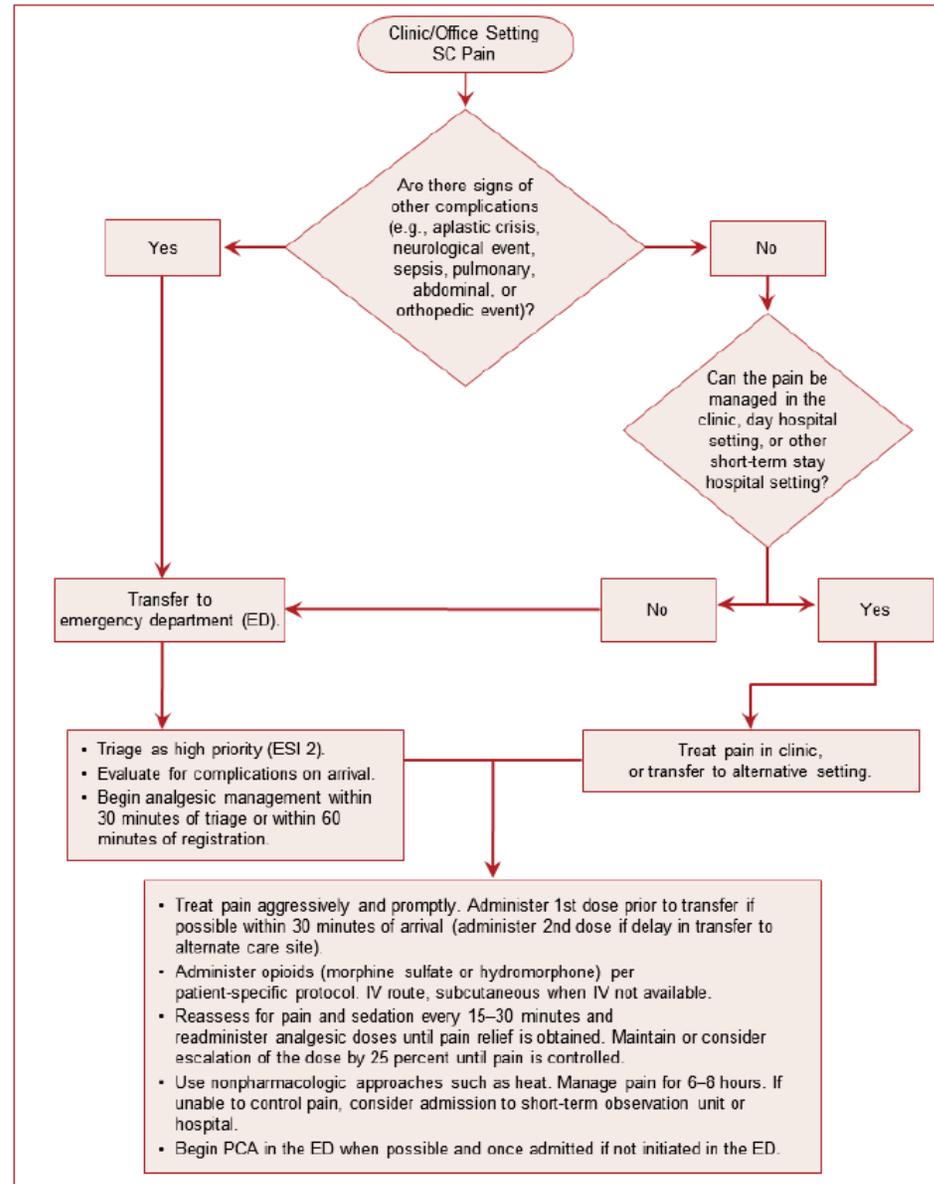
3. In adults and children with SCD and a VOC,
 - Use an individualized prescribing and monitoring protocol (written by the patient's SCD provider) or an SCD-specific protocol whenever possible (see Exhibit 7 below) to promote rapid, effective, and safe analgesic management and resolution of the VOC. **(Consensus-Panel Expertise)**
4. In adults and children with SCD and a VOC associated with mild to moderate pain who report relief with nonsteroidal anti-inflammatory drugs (NSAIDs) in the absence of contraindications to the use of NSAIDs, continue treatment with NSAIDs. **(Moderate Recommendation, Low-Quality Evidence)**
5. In adults and children with SCD and a VOC associated with severe pain, rapidly initiate treatment with parenteral opioids. **(Strong Recommendation, High-Quality Evidence)**
6. In adults and children with SCD and a VOC associated with severe pain,
 - Calculate the parental (IV or subcutaneous) opioid dose based on total daily short-acting opioid dose currently being taken at home to manage the VOC. **(Consensus-Panel Expertise)**
 - Administer parenteral opioids using the subcutaneous route when intravenous access is difficult. **(Consensus-Panel Expertise)**
 - Reassess pain and re-administer opioids if necessary for continued severe pain every 15-30 minutes until pain is under control per patient report. **(Consensus-Adapted)**
 - Maintain or consider escalation of the dose by 25 percent until pain is controlled. **(Consensus-Panel Expertise)**
 - Reassess after each dose for pain relief and side effects. **(Consensus-Panel Expertise)**
 - Initiate around-the-clock opioid administration by patient-controlled analgesia (PCA) or frequently scheduled doses versus "as requested" (PRN) administration. **(Moderate Recommendation, Low-Quality Evidence)**
7. If ordering around-the-clock, continuous infusion of opioids via the PCA, carefully consider whether there is a need to withhold long-acting oral opioids to prevent over-sedation. **(Consensus-Panel Expertise)**
 - If demand dosing only is ordered via the PCA, continue use of long-acting oral opioids **(Consensus-Panel Expertise)**
 - At discharge, evaluate inpatient analgesic requirements, wean parenteral opioids prior to conversion to oral opioids, and adjust home dose of long- and short-acting opioid prescriptions to prevent opioid withdrawal after discharge. **(Consensus-Panel Expertise)**
8. In adults and children with SCD and a VOC, do not use meperidine unless it is the only effective opioid for an individual patient. **(Consensus-Adapted)**
9. In adults and children with a VOC, administer oral NSAIDs as an adjuvant analgesic in the absence of contraindications. **(Consensus-Adapted)**
10. In adults and children with a VOC who require antihistamines for itching secondary to opioid administration, prescribe agents orally, and do not re-administer with each dose of opioid in the acute VOC management phase. Re-administer every 4 to 6 hours if needs. **(Consensus-Panel Expertise)**
11. To reduce the risk of acute chest syndrome in adults and children hospitalized for VOC,
 - Encourage use of incentive spirometry while awake. **(Strong Recommendation, Moderate-Quality Evidence)**
 - Encourage ambulation and activity as soon as possible. **(Consensus-Panel Expertise)**
12. In adults and children with VOC, use adjunctive nonpharmacologic approaches to treat pain such as local health application and distraction. **(Consensus-Adapted)**



13. In euvoletic adults and children with SCD and a VOC who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over-hydration. **(Consensus-Adapted)**
14. In adults and children with SCD and a VOC being treated with opioids, monitor for excessive sedation by measuring sedation with an objective measurement sedation scale and oxygenation levels. **(Consensus-Panel Expertise)**
15. Gradually titrate down parental opioids as VOC resolves. **(Consensus-Panel Expertise)**
16. In adults and children with SCD and a VOC, do not administer a blood transfusion unless there are other indications for transfusion. **(Moderate Recommendation, Low-Quality Evidence)**
17. In adults and children with SCD and a VOC with an oxygen saturation <95 percent on room air, administer oxygen. **(Consensus-Panel Expertise)**



Exhibit 7. Acute Pain Algorithm*



Note: See [recommendation 3](#), page 34.

* These recommendations are intended to be for all settings where patients present with VOC. (Consensus-Panel Expertise)



The **2014 National Heart, Lung, and Blood Institute (NHLBI)** expert panel report recommended the following for managing pain in patients with sickle cell anemia (SCA):

- Educate all patients with sickle cell anemia (SCA) and their family members about hydroxyurea therapy. **(Consensus–Panel Expertise)**
- In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, treat with hydroxyurea. **(Strong Recommendation, High-Quality Evidence)**
- In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea. **(Strong Recommendation, Moderate-Quality Evidence)**
- In adults with SCA who have a history of severe and/or recurrent acute chest syndrome (ACS), treat with hydroxyurea.* **(Strong Recommendation, Moderate-Quality Evidence)**
- In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea. **(Strong Recommendation, Moderate-Quality Evidence)**
- In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia). **(Strong Recommendation, High-Quality Evidence for ages 9–42 months; Moderate Recommendation, Moderate-Quality Evidence for children >42 months and adolescents)**. Note: The panel intentionally used the term "offer" realizing that patients' values and preferences may differ particularly considering treatment burden (e.g., laboratory monitoring, office visits), availability of drug in a liquid form, and cost. Therefore, the panel strongly encourages shared decisionmaking and discussion of hydroxyurea therapy with all patients.
- In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, hydroxyurea therapy can be added to improve anemia. **(Weak Recommendation, Low-Quality Evidence)**
- In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy. **(Moderate Recommendation, Very Low-Quality Evidence)**
- To ensure proper use of hydroxyurea and maximize benefits and safety, use an established prescribing and monitoring protocol. **(Strong Recommendation, High-Quality Evidence)**
- In people with HbS β -thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life, consult a sickle cell expert for consideration of hydroxyurea therapy. **(Moderate Recommendation, Low-Quality Evidence)**
- In people not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult a sickle cell expert. **(Moderate Recommendation, Very Low-Quality Evidence)**



Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and RBC MCV
- Quantitative measurement of HbF if available (e.g., hemoglobin electrophoresis, high-performance liquid chromatography (HPLC))
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring Therapy

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy.
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.
- Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease
- Starting dosage for infants and children: 20 mg/kg/day
- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for a target absolute neutrophil count $\geq 2,000/\mu\text{L}$; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/ μL .
- Maintain platelet count $\geq 80,000/\mu\text{L}$
- If neutropenia or thrombocytopenia occurs:
 - Hold hydroxyurea dosing
 - Monitor CBC with WBC differential weekly
 - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias
- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
 - Increase by 5 mg/kg/day increments every 8 weeks
 - Give until mild myelosuppression (absolute neutrophil count 2,000/ μL to 4,000/ μL) is achieved, up to a maximum of 35 mg/kg/day.
- Once a stable dose is established, laboratory safety monitoring should include:
 - CBC with WBC differential, reticulocyte count, and platelet count every 2–3 months
- People should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
 - Monitor RBC MCV and HbF levels for evidence of consistent or progressive laboratory response.
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy.
- For the patient who has a clinical response, long-term hydroxyurea therapy is indicated.
- Hydroxyurea therapy should be continued during hospitalizations or illness.



In 2015, the **American Academy of Family Physicians (AAFP)** updated the Management of Sickle Cell Disease guideline, adapted from the recommendations from the 2014 Expert Panel Report. The following recommendations were regarding treating pain:

- Initiate rapid treatment with opioids in adults and children with sickle cell disease and a vasoocclusive crisis with severe pain. **(Strong Recommendation, High-Quality Evidence)**
- Continue treatment with NSAIDs for adults and children with SCD who have a VOC associated with mild to moderate pain and who report relief with NSAIDs and do not have contraindications. **(Moderate Recommendation, Low-Quality Evidence)**
- Initiate around-the-clock opioid administration via patient-controlled analgesia or frequently scheduled doses vs. as-needed administration in adults and children with a VOC associated with severe pain. **(Moderate Recommendation, Low-Quality Evidence)**
- Use an individualized prescribing and monitoring protocol (written by the patient's primary physician for SCD care) or an SCD-specific protocol whenever possible to promote rapid, effective, and safe analgesic management and resolution of the VOC in children and adults with SCD (Figure 1 below). **(Consensus)**
- To reduce the risk of ACS, encourage the use of incentive spirometry while awake in adults and children who are hospitalized for a VOC. **(Strong Recommendations, Moderate-Quality Evidence)**
- Do not give blood transfusions to children and adults with a VOC unless there are other indications. **(Moderate Recommendation, Low-Quality Evidence)**



Acute Pain Management in Sickle Cell Disease

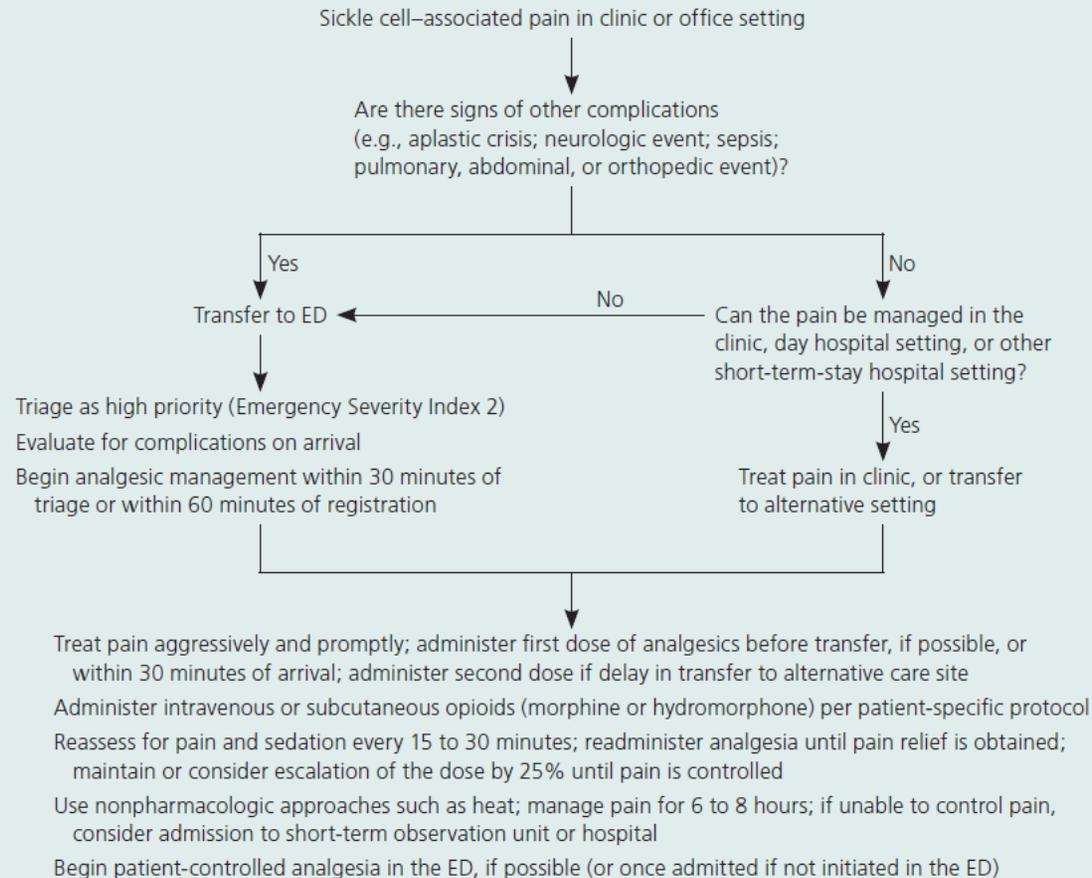


Figure 1. Algorithm for acute pain management in patients with sickle cell disease. (ED = emergency department.)

Adapted from National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease. Expert panel report, 2014. <http://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf>. Accessed September 29, 2015.



American Society of Hematology (ASH) and the **Choosing Wisely** initiative in 2014 recommended to not routinely transfuse patients with sickle cell disease for chronic anemia or uncomplicated pain crisis without an appropriate clinical indication.

ASH is currently developing new clinical practice guidelines on the management of acute and chronic complications of SCD, anticipated release date is 2019

In **2012**, the United Kingdom's **National Institute for Health and Care Excellence (NICE)** released the following recommendations for managing acute painful episodes in hospital:

- Individualized assessment at presentation
 - o Treat an acute painful sickle cell episode as an acute medical emergency. Follow locally agreed protocols for managing painful sickle cell episodes and/or acute medical emergencies that are consistent with this guideline.
 - o Throughout an acute painful sickle cell episode, regard the patient (and/or their carer) as an expert in their condition, listen to their views and discuss with them:
 - The planned treatment regimen for the episode
 - Treatment received during previous episodes
 - Any concerns they may have about the current episode
 - Any psychological and/or social support they may need
 - o Assess pain and use an age-appropriate pain scoring tool for all patients presenting at hospital with an acute painful sickle cell episode
 - o Offer analgesia within 30 minutes of presentation to all patients presenting at hospital with an acute painful cell episode
 - o Clinically assess all patients presenting at hospital with an acute painful sickle cell episode, including monitoring of:
 - Blood pressure
 - Oxygen saturation on air (if oxygen saturation is 95% or below, offer oxygen therapy)
 - Pulse rate
 - Respiratory rate
 - Temperature
 - o Assess all patients with sickle cell disease who present with acute pain to determine whether their pain is being caused by an acute painful sickle cell episode or whether an alternative diagnosis is possible, particularly if pain is reported as atypical by the patient.
- Primary analgesia
 - Ask about and take into account any analgesia taken by the patient for the current episode before presentation



- Ensure that the drug, dose and administration route is suitable for the severity of the pain and the age of the patient
 - Refer to the patient's individual care plan if available
 - Offer a bolus dose of a strong opioid by a suitable administration route, in accordance with locally agreed protocols for managing acute painful sickle cell episodes, to:
 - All patients presenting with severe pain
 - All patients presenting with moderate pain who have already had some analgesia before presentation
 - Consider a weak opioid as an alternative to a strong opioid for patients presenting with moderate pain who have not yet had any analgesia
 - Offer all patients regular paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) by a suitable administration route, in addition to an opioid unless contraindicated
 - Do not offer pethidine for treating pain in an acute painful sickle cell episode
- Reassessment and ongoing management
 - Assess the effectiveness of pain relief:
 - Every 30 minutes until satisfactory pain relief has been achieved, and at least every 4 hours thereafter
 - Using an age-appropriate pain scoring tool
 - By asking questions, such as:
 - How well did that last painkiller work?
 - Do you feel that you need more pain relief?
 - If the patient has severe pain on reassessment, offer a second bolus dose of a strong opioid (or a first bolus dose if they have not yet received a strong opioid)
 - Consider patient-controlled analgesia if repeated bolus doses of a strong opioid are needed within 2 hours. Ensure that patient-controlled analgesia is used in accordance with locally agreed protocols for managing acute painful sickle cell episodes and/or acute medical emergencies
 - Offer all patients who are taking an opioid:
 - Laxatives on a regular basis
 - Anti-emetics as needed
 - Antipruritics as needed
 - Monitor patients taking strong opioids for adverse events, and perform a clinical assessment (including sedation score):
 - Every 1 hour for the first 6 hours
 - At least every 4 hours thereafter
 - If the patient does not respond to standard treatment for an acute painful sickle cell episode, reassess them for the possibility for an alternative diagnosis



- As the acute painful cell episode resolves, follow locally agreed protocols for managing acute painful sickle cell episodes to step down pharmacological treatment, in consultation with the patient
- Possible acute complications
 - Be aware of the possibility of acute chest syndrome in patients with an acute painful sickle cell episode if any of the following are present at any time from presentation at discharge:
 - Abnormal respiratory signs and/or symptoms
 - Chest pain
 - Fever
 - Signs and symptoms of hypoxia:
 - Oxygen saturation of 95% or below or
 - An escalating oxygen requirement
 - Be aware of other possible complications seen within an acute painful sickle cell episode, at any time from presentation to discharge, including:
 - Acute stroke
 - Aplastic crisis
 - Infections
 - Osteomyelitis
 - Splenic sequestration
- Management of underlying pathology
 - Do not use corticosteroids in the management of an uncomplicated acute painful sickle cell episode
- Non-pharmacological interventions
 - Encourage the patient to use their own coping mechanisms (for example relaxation techniques) for dealing with acute pain
- Settings and training
 - All healthcare professional who care for patients with an acute painful sickle cell episodes should receive regular training, with topics including:
 - Pain monitoring and relief
 - The ability to identify potential acute complications
 - Attitudes towards and preconceptions about patients presenting with an acute painful sickle cell episode
 - Where available, use daycare settings in which staff have specialist knowledge and training for the initial assessment and treatment of patients presenting with an acute painful sickle cell episode
 - All healthcare professionals in emergency departments who are for patients with an acute painful sickle cell episode should have access to locally agreed protocols and specialist support from designated centres
 - Patients with an acute painful sickle cell episode should be cared for in an age-appropriate setting



- For pregnant women with an acute painful sickle cell episode, seek advice from the obstetrics team and refer when indicated
- Discharge information
 - Before discharge, provide the patient (and/or their carer) with information on how to continue to manage the current episode, including:
 - How to obtain specialist support
 - How to obtain additional medication
 - How to manage any potential side effects of treatment they have received in hospital

The **2000 American Academy of Family Physicians** recommended the following for pain management for child with sickle cell disease:

- Primary care management
 - Pain: oral hydration, acetaminophen (e.g. Tylenol) with or without codeine, ibuprofen (Advil, Motrin), orally or parenterally administered morphine
- Consultation Recommended
 - Persistent pain in an extremity accompanied by acute signs of classic inflammation, increased temperature or positive blood culture
 - Chest pain accompanied by persistently decreased oxygen saturation and/or radiographic findings
 - Severe or persistent headaches

References:

1. American Society of Hematology (2014). Choosing Wisely Guidelines and Quality Care. Accessed on July 10th, 2018 at <http://www.hematology.org/Clinicians/Guidelines-Quality/502.aspx>
2. Expert Panel Report. Evidence-based management of sickle cell disease. In: U.S. Department of Health and Human Services. Bethesda, MD: National Heart, Lung, and Blood Institute; 2014.
3. National Institute for Health and Clinical Excellence. Sickle cell acute painful episode: management of an acute painful episode in hospital. (Clinical guideline 143.) 2012. <http://guidance.nice.org.uk/CG143>.
4. Wethers, D. L. (2000). Sickle cell disease in childhood: Part I. Laboratory diagnosis, pathophysiology and health maintenance. *American Family Physician*, 62(5), 1013-1020, 1027-1018.
5. Yawn, B. P., & John-Sowah, J. (2015). Management of Sickle Cell Disease: Recommendations from the 2014 Expert Panel Report. *American Family Physician*, 92(12), 1069-1076.



Health System Guidelines

In 2012, **Seattle Children's Hospital** released the following recommendations for pain management in the Sickle Cell Disease Critical Elements of Care Guideline

- 3-Month Check by Comprehensive program/Teaching Goals for Age
 - **Pain Episodes, Sickle Dactylitis:** Discuss how “colic” or fussiness may be symptoms of pain. Discuss administration of liberal oral fluids and appropriate outpatient pain medications. If pain is not relieved by fluids, rest, and oral analgesics, the child should be medically evaluated. Make available resources for coping with pain.
- 4-Month Check by Primary Care Provider
 - Reinforce teaching about fever, splenic size, fluids, antibiotics, folic acid and pain therapy
- 5-Month Check by Comprehensive Program/Teaching Goals for Age
 - Reinforce earlier teaching
- 6-Month Check by Primary Care Provider
 - Reinforce earlier teaching
- 8- to 9-Month Check by Comprehensive/Primary Care Program/Teaching Goals for Age
 - Review and discuss prior teaching
- 11- to 12-Month Check by Comprehensive/Primary Care Program/Teaching Goals for Age
 - Nurse review care plan with family
- 14- to 15-Month Check by Comprehensive/Primary Care Program/Teaching Goals for Age
 - Review past teaching and examination
 - Social service case review
- 17- to 18-Month Check by Comprehensive/Primary Care Program/Teaching Goals for Age
 - Review past teaching and examination
 - Nurse review care plan with family
 - Distribute pain questionnaire
- 21-Month Check by Comprehensive/Primary Care Program/Teaching Goals for Age
 - Review past teaching and examination
 - Social service case review
 - Nurse review care plan with family
- 24-Month Check by Primary Care Provider
 - Routine well-child care, review previous teachings.
- 2 1/2-Year Check by Comprehensive/Primary Care Program/Teaching Goals for Age (Annually on the half year)



- Review need and importance of yearly studies
- Review past teachings
- Introduce concepts of incentive spirometry for lung expansion when sick or during pain episodes. Discuss age appropriate substitutes for incentive spirometry.
- Review status of new potential treatments and interventions
- Nurse review care plan with family
- 3- and 4-Year Check by Primary Care Provider
 - Assess pain status, counsel family on pain management prevention and treatment
 - Begin coping strategy teaching with child
- 5-Year Check by Primary Care Provider
 - Routine well-child care
- 5 ½- and 6 ½- Year Check by Comprehensive Program/Teaching Goals for Age
 - Review past teaching and examination
 - Nurse review care plan with family
 - Reinforce incentive spirometry during pain episodes and illness to prevent acute chest syndrome
 - Review status of new potential treatments and interventions
- Annual check by Primary Care Provider
 - Routine well-child care
 - Review yearly studies
- Annually from age 7 ½ to 13 years on the Half-Year Check by Comprehensive Program/Teaching Goals for Age
 - Review past teaching and examination
 - Monitor/counsel on pain management
 - Nurse review care plan with family
 - Review status of new potential treatments and interventions
 - Assess and teach self-care skills
 - Review yearly studies
 - Screen for depression and discuss coping strategies provide mental health services
- Annually from 14 to 18 years: Adolescence Issues
 - Review past teaching and examination
 - Monitor/counseling on pain management
 - Nurse review care plan with family



- Begin to develop a plan for transition to adult care
- Review yearly studies

General Principles of Pain Management: a number of general principles can be applied to the management of pain in sickle cell disease

- A. Pain must be viewed within a chronic disease continuum: Promotion of wellness and development while also consistently addressing pain is necessary.
- B. Health care professionals have the accountability/responsibility for using a proactive, not a reactive approach. Multiple interventions and approaches should be integrated in the management of pain, not simply medication alone.
- C. Emphasize the value of a system-wide approach.
 - A. Effective pain management is contingent on involvement by administrators, managers, practitioners and family members.
 - B. Role of child and family:
 - To expect that pain be treated/integrated into a plan of treatment
 - To participate in designing and modifying plan, informing providers of personal belief system that impacts care choices
 - To obtain education and support
 - C. Role of administrations, managers, and practitioners:
 - Pain relief is a quality assurance/continuous quality improvement issues for children with chronic illness. Care effectiveness must be evaluated.
 - Develop standards of care/clinical guidelines for common pain problems such as: Emergency room treatment of sickle cell pain episode, home management procedures, and developing multiple healthy coping strategies.
- D. Adequate assessment is the cornerstone of therapy
 - 1. Pain assessment should be developmentally appropriate and a routine part of the inpatient and outpatient care of children with these chronic diseases.
 - 2. The child's complaints of pain should be believed. Verbal self-report is primary and cannot be disputed. (See Sickle Cell Pain Assessment Diagram)
- E. Assess and develop a plan of care with the first episode of pain
 - 1. Online "Pain profiles" that are accessible or transferable, regardless of site of care
 - 2. Summarized pain history and details the pain care plan based on child and family input and past experiences. Plan should include both non-pharmacologic and pharmacologic details. Plan is modified and updated on a real-time basis.
 - 3. Life records: Eliminates the need for repeated questioning of child/parent(s), particular as they enter different hospital areas (ER, clinic, inpatient, OR).
 - 4. A pain problem list should be instituted so that pain stemming from the disease and its treatment can be isolated and treated appropriately.
 - 5. Hand-held records: Empowers child and family.
- F. Guidelines for clinical care
 - 1. Avoid the use of the term pain "crisis" as this can contribute to a sense of anxiety. A more appropriate term is "pain episode." (refer to pain algorithms and charts).
 - 2. General principles of pharmacologic management:



- a. Severe pain is an emergency and must be treated accordingly.
 - b. Use a stepwise approach to pharmacologic therapy that includes: initial therapy with NSAIDs, add low potency short acting opioids if necessary, change to higher potency short acting opioids if needed, add long acting opioids and adjuvant therapies as needed.
 - c. Assessment and re-assessment must be ongoing throughout the course of pain treatment.
 - d. Be certain that adequate analgesics are given to allow nighttime sleep.
 - e. In the majority of cases, oral routes of analgesia are effective and should be used.
 - f. Scheduled administration to prevent anticipated return of pain is appropriate, unless pain is truly episodic and unpredictable.
 - g. Avoid noxious routes of administration (e.g. I.M. injections) since children will often deny pain due to a fear of needles.
 - h. Addiction is rare. Fear of addiction should not restrict adequate opioid administration.
 - i. Do not use placebos.
 - j. Involve the child and his/her family in the treatment, and respect personal preferences and cultural diversity.
 - k. If dose reduction is indicated, it should be done slowly to avoid precipitating severe pain withdrawal.
 - l. Side effects should be anticipated and treated.
 - m. The goal of therapy should be adequate analgesia to allow increased function as determined by the patient, family and staff.
 - n. Although there are guidelines for starting doses, there is no maximum dose for opioids. The right dose is the dose that is adequate to relieve the pain without undue toxicity.
 - o. Access often for respiratory compromise, as hypoxemia may contribute to episodes of acute chest syndrome. Incentive spirometry while on opiates.
3. Complimentary non-pharmacologic strategies-development approaches:

Infants

- Explanations:* Caregiver teaching
Distractions: Music/mobiles, soothing talk, soft of a novel voice, calm demeanor, oral-motor stimulation (pacifiers, non-nutritive sucking)
Containment: Holding/cuddling/swaddling, positioning, pacifier
Physical: Massage (applicability/efficacy being determine)

Toddlers/Preschoolers

- Distraction:* Pop-up books, magic circle/magic game, puppets, kaleidoscopes, counting ABCs, music-sing-along songs, squeezing on koosh ball
Distraction with breathing: Pinwheel, blowing bubbles, “meow-woof” breathing, party blowers
Breathing/Relaxation: “Go limp as a ragdoll,” or “you’re blowing hurt away,” or ask the child to yawn, choo-choo like a train



Imagery: Stories-use images familiar to the child
Explanations: Before procedure, provide concrete and brief explanations to caregiver and child: during procedure, provide sensory information and emphasize informational affective aspects of the experience; after procedure, use therapeutic play
Physical: Massage, heat, acupuncture, acupressure, Transcutaneous Elective Nerve Stimulation (TENS)

School-Age/Adolescents

Modeling/Desensitization: Explanations to child and family
Distraction (younger): Pop-up books; counting ABCs, puppets, kaleidoscopes, music with I-Pod, DVD player, video games
Imagery (older): Pain switch, familiar images with stories, biofeedback



Common Pain States Associated with Sickle Cell Disease

Pain States	Clinical Signs & Symptoms	Signs & Underlying Cause	Special Features & Considerations
Acute Painful Event	<ul style="list-style-type: none"> Sudden onset Pain in any or all parts of the body 	<ul style="list-style-type: none"> Vaso-occlusion Endothelial damage Inflammation 	<ul style="list-style-type: none"> Unpredictable, recurrent Great variability All ages
Acute Hand-Foot Syndrome (Dactylitis)	<ul style="list-style-type: none"> Painful dorsal swelling of hands and feet 	<ul style="list-style-type: none"> Symmetrical infarcts of metacarpal and metatarsal bones due to obstruction of developing blood vessels 	<ul style="list-style-type: none"> More common in childhood Often first manifestation of disease (occurs as early as 6 months of age)
Acute Inflammation of Joints	<ul style="list-style-type: none"> Painful, swollen joints 	<ul style="list-style-type: none"> Vaso-occlusion/injury Inflammation Infected joints Gout 	<ul style="list-style-type: none"> May accompany dactylitis Acute flare-ups as isolated events Septic arthritis is rare but may occur
Acute Chest Syndrome	<ul style="list-style-type: none"> Chest pain, particularly rib and substernal area Chest pain posteriorly (upper back) Fever, tachypnea, and/or hypoxia 	<ul style="list-style-type: none"> Pulmonary infiltrate May be associated with infarction, infection or hemorrhage, or any combination of these Unilateral pain (splinting from atelectasis) 	<ul style="list-style-type: none"> May require transfusion and can be fatal Common cause of mortality in children and adults
Splenic Sequestration	<ul style="list-style-type: none"> Left upper-quadrant pain Marked pallor Sudden decrease in hemoglobin concentration Enlarged spleen 	<ul style="list-style-type: none"> Blood trapped in the spleen 	<ul style="list-style-type: none"> Can be catastrophic in children, with possibility of circulatory collapse Insidious onset in adults Occurs in older children and adults with HbSC and sickle β^+-thalassemia
Intrahepatic Sickling or Hepatic Sequestration	<ul style="list-style-type: none"> Right upper-quadrant pain Sudden decrease in hemoglobin Enlarged liver 	<ul style="list-style-type: none"> Blood pooling in the liver 	<ul style="list-style-type: none"> Occurs more commonly in adults
Abdominal and Intra-abdominal Pain	<ul style="list-style-type: none"> Jaundice Diffuse abdominal pain Enlarged spleen 	<ul style="list-style-type: none"> Cholelithiasis Gastritis Constipation secondary to opioid therapy Splenic infarction 	<ul style="list-style-type: none"> Can be initial manifestation of acute chest syndrome Involve surgery if severe symptoms
Priapism	<ul style="list-style-type: none"> Painful erection 	<ul style="list-style-type: none"> Sickling in sinusoids of penis 	<ul style="list-style-type: none"> May be chronic or stuttering (intermittent)
Avascular Necrosis of Femur or Humerus	<ul style="list-style-type: none"> Prolonged, constant bone pain Shoulder pain Knee pain Hip pain 	<ul style="list-style-type: none"> Associated with bone infarction, sickle arthritis 	<ul style="list-style-type: none"> Physical therapy may be useful for reducing pain and maintaining function
Chronic Neuropathic Pain	<ul style="list-style-type: none"> Pain in back, lower extremities, other sites Spontaneous Lancinating Burning 	<ul style="list-style-type: none"> Older adults: disc disease, infections Collapsed vertebrae Iron overload neuropathy 	<ul style="list-style-type: none"> Must be considered in patients with a decreased response to opioids Physical therapy Consider medications for neuropathic pain such as gabapentin Treatment modalities may require days or weeks before taking effect Creates chronic pain state

Adapted from APS guidelines



Pain Assessment Tools:

There are a variety of tools available to measure pain severity and functional impact. The following are a variety of tools to choose from. The practitioner should use what is most appropriate for the patient and situation.

Assessment Tool 1: The Oucher

Which part of the scale should be used?

If children can count to 100, they can use the numerical scale; if not, they should use the photographic scale.

How does one use the Oucher?

- A. Let children practice using the Oucher.
 1. Ask them to recall times they hurt in the past.
 2. Have them describe these episodes to you and then rate them on the Oucher.
- B. Collect data and convert to scores.
 1. After re-explaining the scale, ask “How much hurt do you have right now?”
 2. If the child uses the numerical scale, the number they give is the Oucher score; if the child uses the photographic scale, the picture they select is converted to the appropriate predetermined score known on the oucher (0, 20, 40, 60, 80 or 100).

Assessment Tool 2: Pain Intensity Number Scale

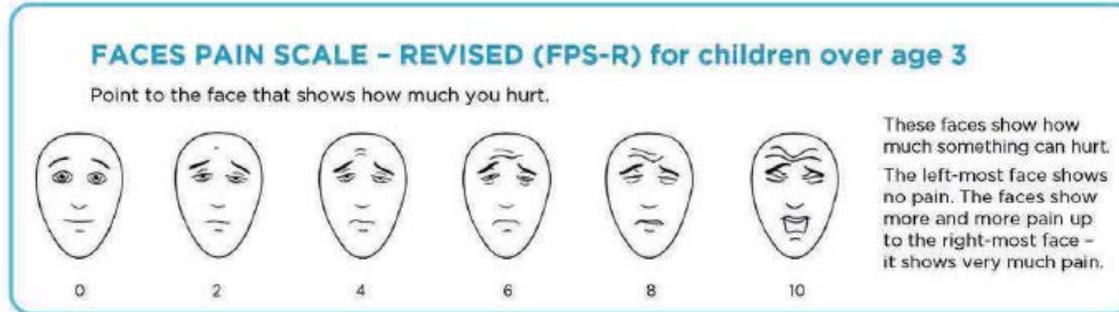
Children Developmentally Later School-Age and Adolescent

Instructions:

1. “I need to know how much pain you have because I can’t feel your pain. I want you to use a scale so you can tell me how much pain you have right now.”
2. The numbers between 0 and 10 represent all the pain a person could have. Zero means no pain and 10 means pain as bad as it could be. You can use any number between 0 and 10 to let me know how much you have right now.”
3. “Give your pain a number between 0 and 10 so I will know the intensity of the pain you feel now.”
4. Record the pain intensity on the nursing flow sheet as 0/10, 1/10, 2/10, etc.
5. For younger children, substitute the FACES pain scale for number scale.



Pain Intensity FACES Scale



Assessment Tool 3: Work Graphic Rating Scale

Children Developmentally Later School-Age and Adolescent

Instructions:

1. Place a straight-up-and-down mark on this line to show how much pain you have.

No pain Little pain Medium pain Large pain Worst possible pain

2. Record the pain intensity on the nursing flow sheet as “none,” “little,” “medium,” “large” or “worst possible.”

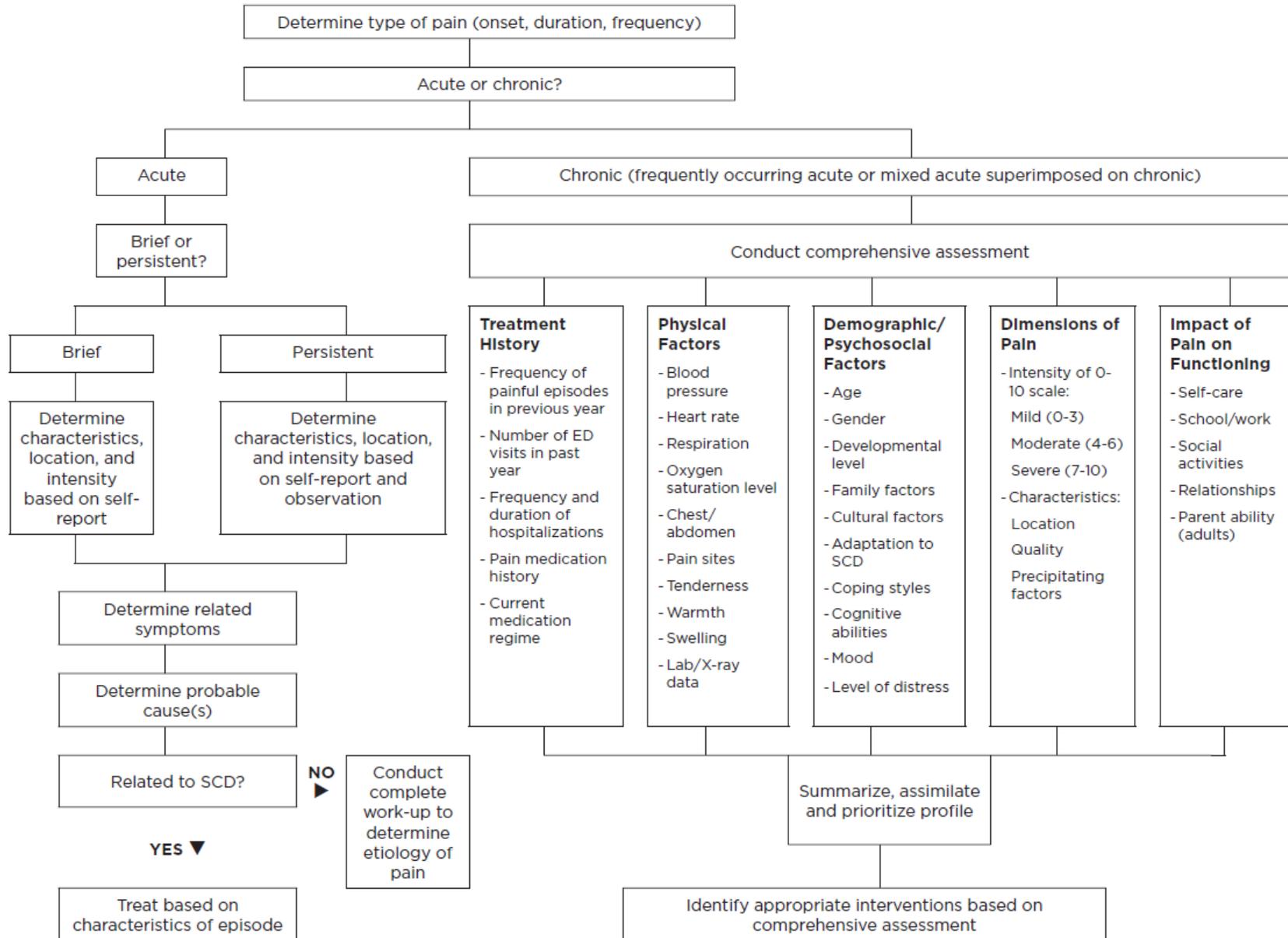
Assessment Tool 4: Functional Assessment

Record functional assessment of pain on flow sheet, for example:

- “Unable to sit up or walk”
- “Able to eat”
- “Able to do self care”

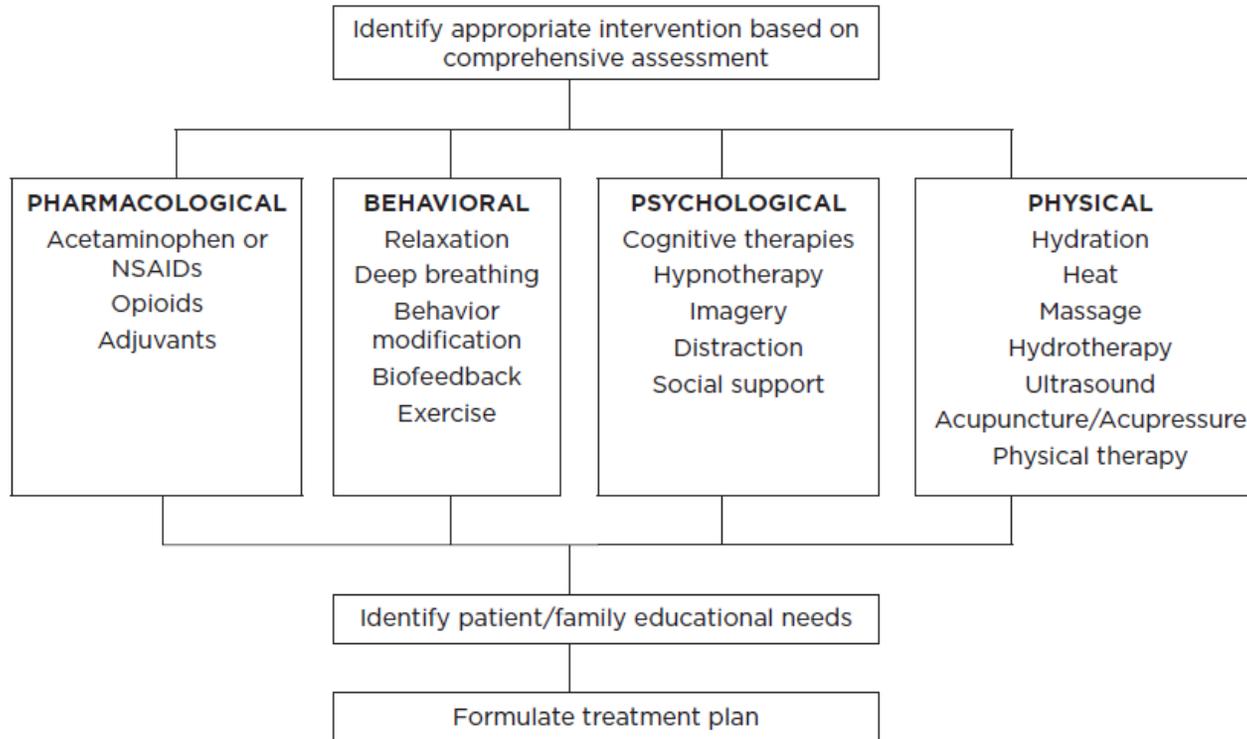


Sickle Cell Pain Assessment





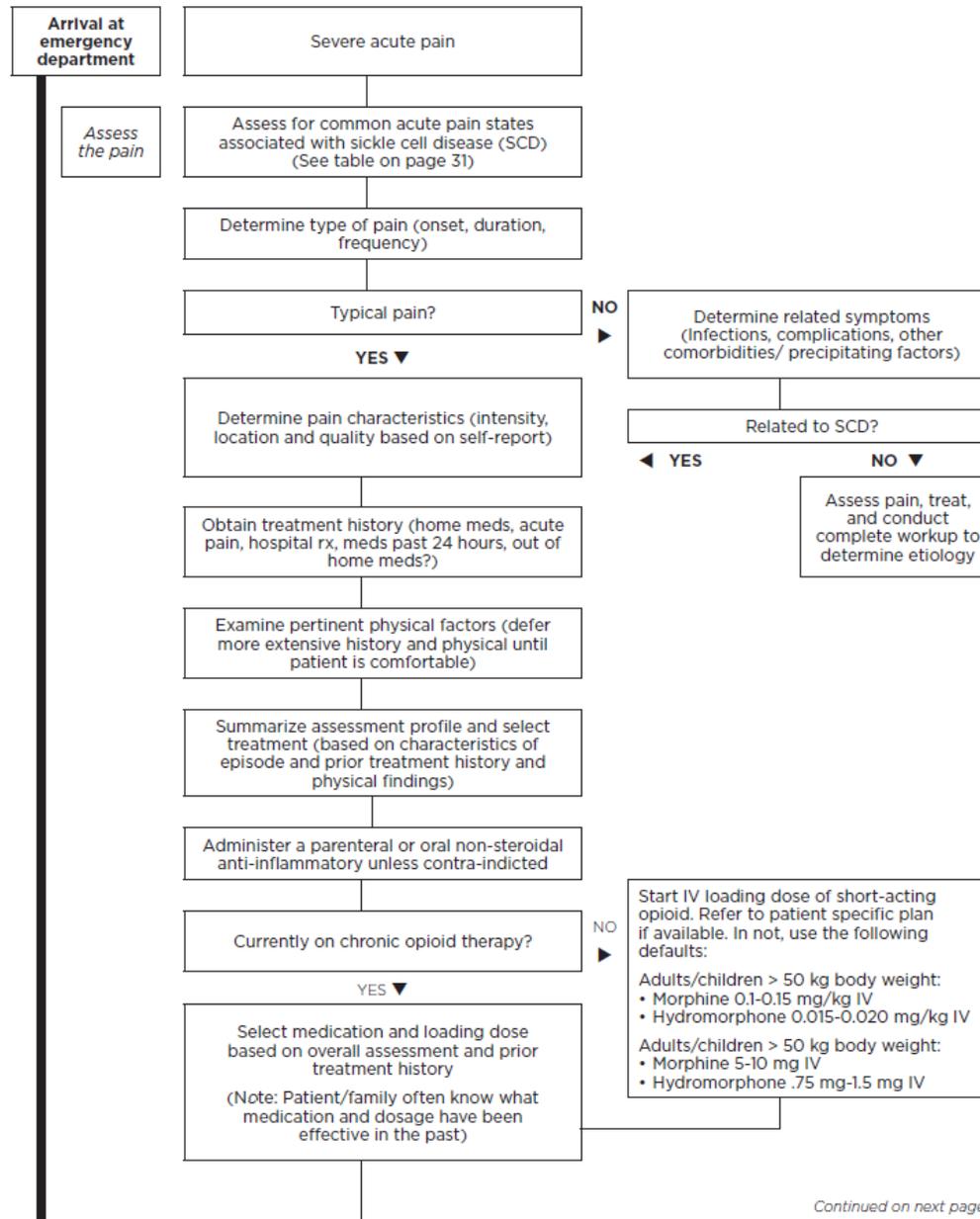
Treatment Flowchart



Adapted from APS guidelines



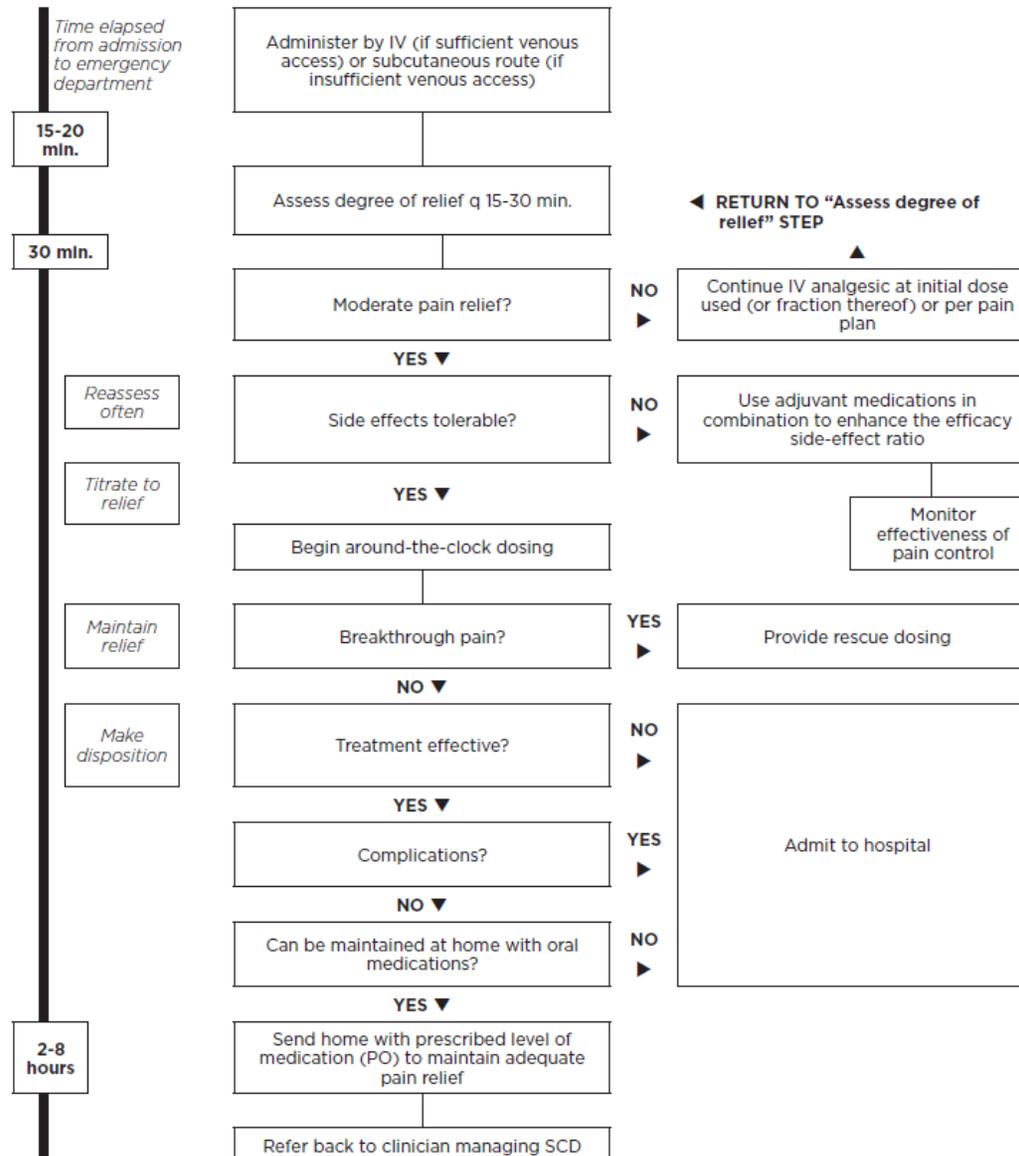
Management of an Episode of Acute Pain in Sickle Cell Disease



Continued on next page



Management of an Episode of Acute Pain in Sickle Cell Disease *Continued from previous page*



These are the American Pain Society guidelines. Individual institutions, including Seattle Children's Hospital, may have differing practices.

Adapted from APS guidelines



Vaso-Occlusive Pain

Diagnosis	Monitoring	Diagnostic (if not previously obtained)	Fluids, Nutrition, General Care	Medications/Treatments	Discharge Criteria
Vaso-occlusive pain in a child with sickle cell disease	<ol style="list-style-type: none"> Vital signs q 4 hr Record I + O, daily weight Continuous pulse ox. if any respiratory symptoms present, or if on parenteral opiates Consider CR monitor 	<ol style="list-style-type: none"> CBC, diff., plt count and retic count initially (compare with patient's baseline data); consider a hold tube for the blood center (for later type and cross) if severe anemia suspected or transfusion anticipated CXR: low threshold if cough or any respiratory signs or symptoms are present, or develop after admission; encourage incentive spirometry prior to CXR Blood culture if >38.2°C; urinalysis, urine culture and other cultures (e.g. CSF) as indicated Consider diagnostic tests to evaluate possible non-sickle causes of pain (e.g. abdominal ultrasound, liver function tests for RUQ to R/O cholelithiasis and cholecystitis) 	<ol style="list-style-type: none"> IV + PO 1.25 x maintenance. Increased fluids only if patient is dehydrated and/or insensible losses are increased (e.g. persistent fever); avoid excessive fluids, which may worsen respiratory status Avoid IV fluid bolus unless clinically dehydrated or clinically indicated (not for pain alone) Incentive spirometry—10 breaths q 2 hr. from 0800-2200 and while awake. Encourage ambulation and activity 	<ol style="list-style-type: none"> Follow patient-specific care plan if available; if not, follow generic steps below Offer heat pads, imagery, relaxation methods or other comfort measures as adjunct to pharmaceuticals. A parenteral or oral non-steroidal anti-inflammatory agent if no contraindication (i.e. gastritis, ulcer or renal impairment) If no established pain plan: Morphine sulfate 0.1 mg/kg/dose IV q 2 hr. or 0.01-0.1 mg/kg/hr. continuous infusion or via PCA (doses above 0.1 mg/kg/hr. may be required but should be used with caution); alternative analgesics may be used in individual cases* Reassess pain control at least twice daily and after every intervention; analgesics may be weaned as tolerated by decreasing dose, not by prolonging interval between doses; discuss analgesic changes with patient/family Start oral opiates as soon as tolerated from a gastrointestinal standpoint, even if requiring IV opiates Consider pain team consultation Ceftriaxone 75mg/kg q 24 hr if febrile (prophylactic penicillin may be discontinued while on broad-spectrum antibiotics) Continue prophylactic folic acid, if applicable O₂ by nasal cannula as needed to keep O₂ saturation > 93% Colace or laxative to prevent narcotic-induced constipation See other Clinical Care Paths for acute chest syndrome, acute anemia crisis, stroke, priapism, if present Avoid use of ice or cold packs 	<ol style="list-style-type: none"> Taking oral fluids well and able to take all PO meds (e.g. prophylactic penicillin) if applicable Adequate pain relief on oral analgesics Afebrile >24 hr and negative cultures >24 hours if applicable Resolution of any pulmonary symptoms or documentation of adequate oxygenation on room air

* These are the American Pain Society guidelines. Individual institutions, including Seattle Children's Hospital, may have differing practices.

Modified from Mountain States Regional Genetic Services Network, 1996



Sedation Scale and Indications for Action*

Sedation Scale		Action Required
S	Sleeping, easily aroused	None Consider monitoring O ₂ saturation
1	Awake and alert	None Consider monitoring O ₂ saturation
2	Occasionally drowsy, easy to arouse	None Consider monitoring O ₂ saturation
3	Frequently drowsy, arousable, drifts off to sleep during conversations	Physically stimulate Decrease or discontinue the opioid Monitor O ₂ saturation
4	Somnolent, minimal or no response to stimuli	Discontinue opioid and consider titration of naloxone Monitor O ₂ saturation

* Adapted from: McCaffery, M., & Pasero, C.L. (1999) Pain: Clinical Manual (2nd ed.). St. Louis: Mosby, Inc.

Note: The above scale and recommendations are not appropriate for patients who are terminally ill, have developed a tolerance to respiratory depression, or in whom sedation is not caused by opioids.



NSAIDs Dosing Data

Medication	Usual Dose for Adults and Children ≤50 kg Body Weight	Usual Dose for Children ¹ and Adults ² ≤50 kg Body Weight
Acetaminophen and Over-the-Counter NSAIDs		
Acetaminophen ³	650 mg q 4 hr 975-1,000 mg q 6 hr	10-15 mg/kg q 4 hr (oral) 15-20 mg/kg q 4 hr (rectal)
Ibuprofen	400-800 mg q 6 hr	10 mg/kg q 6-8 hr ⁴
Ketoprofen (Orudis)	25-75 mg q 6-8 hr	0.5 mg/kg q 6 hr
Naproxen (Naprosyn)	500 mg initially, then 250 mg q 6-8 hr	5-7 mg/kg q 8-12 hr
Naproxen sodium (Anaprox)	550 mg initially, then 275 mg q 6-8 hr	
Parenteral NSAIDs		
Ketorolac tromethamine ^{5, 6} (Toradol)	30 mg initially, then 15-30 mg q 6 hr, parenteral dose not to exceed 5 days or 120 mg/day	0.5 mg/kg q 8 hr intravenously ^{5,6}

¹ Only medications that are FDA-approved as analgesics for children are included.

² Acetaminophen and NSAID dosages for adults weighing less than 50 kg should be adjusted for weight.

³ Acetaminophen lacks the peripheral anti-inflammatory and antiplatelet activities of other NSAIDs.

⁴ Ibuprofen is not FDA-approved for use in children as an over-the-counter medication. It has FDA approval for use in children as a prescription medication for fever; however, some clinicians have had experience in prescribing ibuprofen for pain relief in children.

⁵ For short-term use only.

⁶ Has the same GI toxicities as oral NSAIDs. Safety and efficacy not established for use in children.

Modified from "Guidelines for the Management of Acute and Chronic Pain in Sickle Cell Disease," American Pain Society, August 1999. These are the American Pain Society guidelines. Individual institutions, including Seattle Children's Hospital, may have differing practices.



Opioid Dosing Table

(For patients without established pain plan)

Opioid Agonist	Approx Equianalgesic Oral Dose	Approx Equianalgesic Parenteral Dose	Recommended Starting Dose (Adults > 50 kg) Oral	Recommended Starting Dose (Adults > 50 kg) Parenteral	Recommended Starting Dose (Children, adults < 50 kg) ¹ Oral	Recommended Starting Dose (Children, adults < 50 kg) ¹ Parenteral
Morphine ²	30 mg a 3-4 hr (around-the-clock dosing); 60 mg q 3-4 hr (single dose or intermittent dosing)	10 mg q 3-4 hr	10-30 mg q 3-4 hr	5-10 mg q 2-4 hr	0.3 mg/kg q 3-4 hr	0.1 mg/kg q 3-4 hr
Codeine ³	200 mg q 3-4 hr		15-60 mg q 3-4 hr	Not recommended	0.5-1 mg/kg q 3-4 hr	Not recommended
Hydromorphone ² (Dilaudid)	7.5 mg q 3-4 hr	1.5 mg q 3-4 hr	6 mg q 3-4 hr	1.5 mg q 3-4 hr	0.06 mg/kg q 3-4 hr	0.015 mg/kg q 3-4 hr
Oxycodone	30 mg q 3-4 hr	Not available	10 mg q 3-4 hr	Not available	0.15-0.2 mg/kg q 3-4 hr	Not available
Opioid Agonist - Antagonist and Partial Antagonist						
Nalbuphine (Nubain)	Not available	10 mg q 3-6 hr	Not available	10 mg q 3-6 hr	Not available	0.1 mg/kg q 3-6 hr

Note: Tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient: Titration to clinical response is necessary. Because there is not complete cross-tolerance among these drugs, it is usually necessary to use a lower than equianalgesic dose when changing drugs and to retitrate to response.

Caution: Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting drug metabolism and kinetics.

¹ Caution: Doses listed for patients with body weight less than 50 kg cannot be used as initial starting doses in babies less than 6 months of age. Consult *Clinical Practice Guideline for Acute Pain Management: Operative or Medical Procedures and Trauma section on management of pain in neonates for recommendations.*

² For morphine (hydromorphone and oxymorphone), rectal administration is an alternate route for patients unable to take oral medications, but equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

³ Caution: Codeine doses above 65 mg often are not appropriate due to diminishing incremental analgesia with increasing doses, but continually increasing constipation and other side effects.

Caution: Doses of aspirin, ibuprofen and acetaminophen in combination opioid/NSAID preparations should be avoided to prevent inadvertent toxicity from the non-opiate component.

These are the American Pain Society guidelines. Individual institutions, including Seattle Children's Hospital, may have differing practices.



Acute Chest Syndrome

Diagnosis	Monitoring	Diagnostic (if not previously obtained)	Fluids, Nutrition, General Care	Medications/ Treatments	Discharge Criteria
<p>Definition: A new infiltrate on CXR in a patient with sickle cell disease.</p>	<ol style="list-style-type: none"> Vital signs q 2-4 hr. Continuous pulse oximetry. Consider CR monitor. Record I + O, daily weight 	<ol style="list-style-type: none"> CBC, diff., platelet count and reticulocyte count initially and daily until improving (compare with patient's baseline values). CXR. Repeat for clinical deterioration looking for progression. May need serial CXRs. Type and cross match (minor-antigen-matched if available, sickle negative, leukocyte depleted RBC) to have blood available. Obtain red cell extended phenotyping for sickle cell patients if not done previously (at a minimum type for RhD, Cc, Ee and Kell). Blood cultures if T > 38.2°C or history of recent fever. Capillary or arterial blood gas and assessment by PICU team for severe illness. 	<ol style="list-style-type: none"> Maintain "euvoemia." IV + PO 1-1.25 x maintenance. More fluid is appropriate only if patient is dehydrated or if insensible losses are increased (e.g. persistent fever). Incentive spirometry x 10 breaths q 2 hr. during the day (0800-2200), if awake at night, and prior to all CXRs. Encourage ambulation, activity. 	<ol style="list-style-type: none"> Oxygen to maintain O₂ saturation > 93% Ceftriaxone 75mg/kg Q 24 hr. IV. (Prophylactic penicillin may be discontinued while on broad-spectrum antibiotics.) Azithromycin 10mg/kg PO x1, then 5 mg/kg PO QD days 2-5, or other macrolide antibiotic. Chest physical therapy if consolidation is present. Follow patients specific pain plan. If not available consider morphine 0.1 mg/kg IV q 2 hr. or 0.01 - 0.1 mg/kg/hr. continuous infusion or PCA for severe pain. Alternative analgesics (but not demerol) may be used in individual cases. Adequate pain relief is essential to avoid splinting improve respiratory dynamics that worsens respiratory status. Consider round the clock bronchodilators, especially if patient has history of wheezing or asthma. Some patients benefit even if not clinically obstructed. Consider use of BiPAP or CPAP if not improving with routine measures. Consider red cell transfusion for progressive respiratory decline despite incentive spirometry and #1-6 above. Pain control and incentive spirometry are commonly under-utilized. Transfuse initially if severely ill. <ol style="list-style-type: none"> Simple transfusion to a HCT of 30% (no clear benefit to exchange transfusion). Exchange transfusion for patients with progressive disease and a Hct > 27% or lack of improvement > 36 hrs post simple transfusion. Target a Hct of 30% and Hb S or Hb S + C < 30 %. (May require transfer to ICU for erythrocytapheresis). Remove femoral or central venous catheters as soon as possible after exchange transfusion to reduce risk of thrombosis. See other Clinical Care Paths for acute anemic crisis, stroke, priapism, if present. Continue prophylactic folic acid, if applicable. 	<ol style="list-style-type: none"> Off O₂. Afebrile > 24 hr and negative cultures for 24 hours (if applicable). Good oral intake, able to take all oral medications including antibiotics. Adequate pain relief (if needed) with oral analgesics. Discharge instruction completed regarding home use of incentive spirometry while on opiates. Follow-up plans coordinated with hematology service. CXR to establish new baseline in 2-3 months.



General Anesthesia and Surgery

Pre-Op Evaluation	Pre-Op Transfusion and Pulmonary Care	Intraoperative	Post-Operatives
<ul style="list-style-type: none"> • Baseline CXR, pulse ox, CBC, retic, U/A • Consider pulmonary function tests and/or ECHO for patients with prior history of acute chest syndrome, suspicion of chronic lung disease or decreased exercise performance • Coordination of peri-operative plan with Hematology, Surgery and Anesthesia 	<ul style="list-style-type: none"> • Patient typically admitted the day before for transfusion and hydration while NPO • Simple transfusion targeting a Hct of 30-33% should be strongly considered for all children with Hb SS or Sβ⁰-thalassemia prior to any procedure requiring general anesthesia • Surgery without pre-op transfusion in children with HbS/S and Sβ⁰-thalassemia may be considered in selected cases non- or minimally-invasive procedures (e.g. PE tubes or MRI/MRA). Note: tonsillectomy and/or adenoidectomy is not considered a minor procedure. Recommendations for patients with Hb S/C and Sβ⁺-thalassemia vary. In general, transfusion is not required for smaller procedures such as tonsillectomy and/or adenoidectomy, but transfusion is required for abdominal surgery. Due to a high baseline HCT, these patients often require exchange transfusion. • Use antigen-matched if available, sickle-negative, leukocyte-depleted PRBC (at a minimum RhD, Cc, Ee and Kell) • Practice incentive spirometry or developmentally appropriate substitute (e.g. bubbles) • If history of obstructive disease, start steroid inhaler 3 days before and scheduled albuterol the night before surgery • IV hydration 1-1.25 x maintenance while NPO before procedure. Hold while receiving blood transfusion. 	<ul style="list-style-type: none"> • Minimum 50% O₂ with anesthetic agent • Avoid hypoxia (continuous pulse ox), hypercarbia, or hyperventilation • Avoid tourniquets 	<ul style="list-style-type: none"> • O₂ by nasal cannula at 2 L/min and continuous pulse ox even if O₂ saturations are high. Continue O/N and assess the next day. Maintain saturations >93%. • Document O₂ saturations on room air intermittently to screen for increasing O₂ need. • Encourage early ambulation, activity • IV + po 1-1.25 x maintenance. Avoid excessive hydration, which may precipitate acute chest syndrome. • Strict adherence incentive spirometry: 10 breaths q 2 hr while awake. Use of pain medication before this may be useful.

Modified from Mountain States Regional Genetic Services Network, 1996



2016 Virginia's Sickle Cell Disease Crisis Guideline

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 ad lib and encouraged to ambulate. If patients are known or suspected user of illegal substances and have a PCA and/or IV, they should not 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' O2 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 \geq 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.



Substance	Detection time
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.



Virginia Premier Health Plan Attachments:

SAMPLE ADMISSION ORDERS – SICKLE CELL DISEASE

DIAGNOSIS: SS SC S-β⁺ THAL S-β⁰ 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/ _____ M²/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.

- ☉ Acetaminophen 10-15mg/kg/dose x ____kg = ____mg PO Q6hr (max dose 4 gm/day)
- ☉ Morphine 0.1 – 0.2 mgs/kgs/dose X ____kgs. = ____mgs ☉ IV ☉ IM
☉ SQ Q2-4H prn pain.
- ☉ Morphine (Immediate release) 0.2-0.5 mgs/kgs./dose X ____kgs = ____tabs PO Q2-4H prn pain. (☉ 10 mgs/5cc ☉ 20mgs/5 cc ☉ 10 mgs tab ☉ 20 mgs tab)
- ☉ Morphine (Sustained release) 0.3-0.6 mgs/kgs/dose X ____kgs = ____tabs PO Q8-12H prn pain. (☉ 15 ☉ 30 ☉ 60 ☉ 100 mg. tab)
- ☉ 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):

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

PRN Medications:

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

ANTIBIOTICS:

1. Pen V-K: ☐ 125mg ☐ 250mg PO BID.
2. ☐ Ceftriaxone 50-75mg/kg/24 hrs. x ____kg = ____mgs. IM/IV
Q12-24 hrs.(max. single dose: 2.0 gms)
☐ 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



Primary Literature

NHLBI Systematic Review: Summary of the Evidence

Thirty-two RCTs with more than 1,800 people of all ages, 34 observational studies, and 30 case reports were considered eligible. Because many of these studies evaluated pharmacologic agents that did not decrease pain or significantly reduce length of hospital stay (e.g., poloxamer 188, flusol, vasodilators, methylprednisone, oxygen, urea, and other agents), and which are not approved by the U.S. Food and Drug Administration (e.g., inhaled nitrous oxide, transfusion, etc.), recommendations regarding these agents were not made. One study evaluated the effectiveness of meperidine versus placebo or other opioids and found meperidine more effective than placebo in reducing pain. However, due to the neurotoxicity associated with meperidine, the panel did not make recommendations for its use. **Evidence from several RCTs and observational studies supports the use of opioid therapy in treating VOCs. Indirect, high-quality evidence from populations without SCD also supports the use of opioids in treating VOCs.** A recent report from the American Pain Society (APS) suggests opioids are not effective in treating chronic non-cancer pain. It is important to understand that an acute VOC is considered acute, not chronic pain, and opioids are indicated and should be used to treat pain.

Evidence from RCTs and observational studies supporting the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was conflicting, but overall, the evidence supports their efficacy in reducing pain and decreasing length of hospital stay. Several RCTs and observational studies support the use of around-the-clock dosing of analgesics versus intermittent analgesic administration in treating VOCs. The largest study on this topic, a prospective observational study in Saudi Arabia, included 1,154 people and examined the effect of a pain management protocol. The study found that around-the-clock analgesic infusions for the first 24 hours after admission were more effective for managing VOCs than “on demand” or patient-requested infusions of analgesics. People treated with around-the-clock analgesics achieved a higher discharge rate within 72 hours of admission (83 percent), compared with people who received intermittent (per patient request) analgesics (71 percent). Other observational studies supported these findings and also suggested a more rapid resolution of VOCs and a strong patient preference for around-the-clock analgesic infusions. **The evidence base was insufficient to make specific analgesic dosing recommendations or recommendations for several nonpharmacologic approaches (including oxygen, inhaled nitrous oxide, electrical nerve stimulation, acupuncture, biofeedback, and a day hospital program). In general, the quality of the available evidence was moderate to low.**

References:

1. Expert Panel Report. Evidence-based management of sickle cell disease. In: U.S. Department of Health and Human Services. Bethesda, MD: National Heart, Lung, and Blood Institute; 2014.

Pain Management in Adults						Low Quality Rating if: <input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied) <input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in
Modality: Adjuvant Intravenous Lidocaine						
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations	
Journal: <i>J Pain Palliat Care Pharmacother</i> Author: Nguyen, N.L. Year Published: 2015	Aim: To evaluate the efficacy and safety of adjuvant intravenous (IV) lidocaine in adults	Inclusion Criteria: Patients with past orders for IV lidocaine products. Patients were	Methods: Data extraction consisted of information documented during the regular course of medical	Results: Clinical improvement in pain scores from pre-lidocaine challenge to 24 hours	Study Limitations: <input checked="" type="checkbox"/> None Non-Randomized Studies	



<p>Location: Virginia Commonwealth University Health System/Medical College of Virginia Hospitals</p>	<p>with sickle cell disease (SCD) Study Type: Retrospective Review Size: 11 patients were identified, yielding 15 IV lidocaine trials</p>	<p>included if they were 18 years of age or older, had received at least one IV lidocaine infusion, and had SCD. Exclusion Criteria: Patients who were prisoners or pregnant.</p>	<p>treatment, which included age, gender, race, weight, and parameters specific to IV lidocaine treatment. The amount of opioid medication received by patients were collected and standardized by conversion to morphine dose equivalent (MDE) using the NCCN guidelines. Pain intensity scores, based on numeric pain rating scale of 0 to 10, with 10 being the worst possible pain, were recorded at pre-, post-, and 24 hours post-lidocaine challenge. Additionally, seizure history, cardiovascular history, and alpha-blocker or beta-blocker use were recorded for safety analysis. All data collected were retrieved from electronic and paper medical records at our institution.</p>	<p>post-lidocaine challenge, defined by $\geq 20\%$ reduction in pain scores, was achieved in 53.3% (8 of 15) of IV lidocaine challenges. Of the 8 clinically successful trials, the mean reduction in morphine dose equivalents (MDE) from 24 hours pre-lidocaine challenge to 24 hours post-lidocaine challenge was 32.2%. Additionally, clinically successful trials had a mean initial and a maximum dose of 1 mg/kg/h (range: 0.5–2.7 mg/kg/h) and 1.3 mg/kg/h (range: 0.5–1.9 mg/kg/h), respectively. On average, these patients underwent 3 dose titrations (range: 1–8) and received lidocaine infusions for 4.4 days (range: 2–8 days). Two patients experienced disorientation and dizziness.</p>	<p><input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline</p>	<p>regard to population, intervention, comparison, or outcome) <input checked="" type="checkbox"/> Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain) <input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found) Increase Quality Rating if: <input type="checkbox"/> Large effect <input type="checkbox"/> Dose-response gradient <input type="checkbox"/> Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very Low</p>
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TABLE 3. Morphine dose equivalent (MDE) for clinically successful IV lidocaine trials*

Patient number	MED† 24 hours pre-lidocaine challenge (mg)	MED† 24 hours post-lidocaine challenge (mg)	MDE percent change (%)
1-A*	15,960	4230	-73.6
2-A	26,460	15,460	-41.6
2-B	21,960	16,460	-24.6
3	1660	990	-39.8
10-A	13,100	2400	-77.4
10-B	2500	500	-80.0
10-C	1320	1000	-23.5
11	3914	2550	-35.0
Mean	9434.6	5937.8	-37.2

*Eight IV lidocaine trials were identified as clinically successful (percent reduction in pain score pre vs. 24 hours post-lidocaine challenge $\geq 20\%$). The respective dose equivalent (MDE) for these trials are listed in this table.
†MDE, based on NCCN Guidelines version 1.2015 for Adult Cancer Pain.¹¹
*Patients with more than one admission during the review period have alphabetical letters to differentiate each admission.

References:
1. Nguyen, N. L., Kome, A. M., Lowe, D. K., Coyne, P., & Hawks, K. G. (2015). Intravenous Lidocaine as an Adjuvant for Pain Associated with Sickle Cell Disease. *J Pain Palliat Care Pharmacother*, 29(4), 359-364. doi:10.3109/15360288.2015.1082009



Pain Management in Pediatrics					
Modality: Lidocaine Patches					
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Journal: <i>Pain Practice</i> Author: Rousseau, V., et al. Year Published: 2018 Location: Centre Hospitalier Pierre Oudot, Bourgoin-Jallieu Cedex, France	<p>Aim: To assess the efficacy and tolerance of lidocaine 5% patches in pediatric inpatients</p> <p>Study Type: Prospective, multicenter, single-arm study</p> <p>Size: 40 patients in 4 pediatric French centers.</p>	<p>Inclusion Criteria: Children and young adults of 6 to 21 years of age suffering from either neuropathic pain in an oncologic setting, or localized and superficial pain due to vaso-occlusive bone crises in sickle cell patients, insufficiently relieved by the commonly used treatments (level II or III analgesics, and/or anti-epileptics, and/or neuroleptics). The DN4 score had to be ≥ 4</p> <p>Exclusion Criteria: Glasgow score < 12, clinical conditions not allowing visual analog scale (VAS) self-assessment, a wide painful area with regard to body surface area (i.e. greater than the recommended surface of 1 patch for a body surface area of < 1 m², of 2 patches for a body surface area between 1 and 1.5 m², or of 3 patches for a body surface area of > 1.5 m²), and any contraindication for the use of lidocaine 5% patch as defined in summary of product characteristics.</p>	<p>Methods: Lidocaine 5% patches were used for 6- to 21-year-old pediatric patients suffering from neuropathic pain or superficial bone vaso-occlusive crises. Patches were applied on the painful area for 12 hours a day. The primary endpoint was the proportion of inpatients with significant pain relief defined as a decrease of at least 2 points on the visual analog pain scale (VAS) measured at 12 hours after patch placement over at least 2 consecutive days.</p>	<p>Results: The 12-hour VAS score decreased by at least 2 points over 2 consecutive days in 48.6% of patients 95% unilateral confidence interval (33.8%). Only 7.7% of patients experienced grade 1 or grade 2 toxicities.</p>	<p>Study Limitations:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> None <input type="checkbox"/> Non-Randomized Studies <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline

Low Quality Rating if:

- Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied)
- Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)
- Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)
- Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)

Increase Quality Rating if:

- Large effect
- Dose-response gradient
- Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

- High
- Moderate
- Low
- Very Low

References:



- Rousseau, V., et al. (2018). "Efficacy and Tolerance of Lidocaine 5% Patches in Neuropathic Pain and Pain Related to Vaso-occlusive Sickle Cell Crises in Children: A Prospective Multicenter Clinical Study." *Pain Practice* 18(6): 788-797.

Pain Management in Adults					
Modality: Intravenous (IV) ketamine-midazolam					
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Journal: <i>Journal of Pain & Symptom Management</i> Author: Tawfic, Q.A., et al. Year Published: 2014 Location: 2014	Aim: To study the role of low-dose intravenous (IV) ketamine-midazolam combination in the management of severe painful sickle cell crisis Study Type: Retrospective study Size: 9 patients	Inclusion Criteria: Adult patients who were admitted to the ICU solely for pain management.	Methods: A retrospective analysis was performed with data from adult patients who were admitted to the intensive care unit with severe painful sickle cell crises not responding to high doses of IV morphine and other adjuvant analgesics. A ketamine-midazolam regimen was added to the ongoing opioids as an initial bolus of ketamine 0.25 mg/kg, followed by infusion of 0.2e0.25 mg/kg/h. A midazolam bolus of 1 mg followed by infusion of 0.5e1 mg/h was added to reduce ketamine emergence reactions. Reduction in morphine daily requirements and improvement in pain scores were the determinants of ketamine-midazolam effect. The t-tests were used for statistical analysis.	Results: Mean age of patients was 27 +/- 11 years. Morphine requirement was significantly lower after adding the IV ketamine-midazolam regimen. The mean SD IV morphine requirement (milligram/day) in the preketamine day (D0) was 145.6 +/- 16.5, and it was 112 +/- 12.2 on Day 1 (D1) of ketamine treatment (P = 0.007). The Numeric Rating Scale scores on D0 ranged from eight to ten (mean 9.1), but improved to range from five to seven (mean 5.7) on D1. There was a significant improvement in pain scores after adding ketamine-midazolam regimen (P = 0.01).	Study Limitations: <input type="checkbox"/> None Non-Randomized Studies <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input checked="" type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input checked="" type="checkbox"/> Differences in important prognostic factors at baseline

Low Quality Rating if:
 Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied)
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Increase Quality Rating if:
 Large effect
 Dose-response gradient
 Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
 High
 Moderate
 Low
 Very Low

References:



1. Tawfic, Q. A., et al. (2014). "The role of a low-dose ketamine-midazolam regimen in the management of severe painful crisis in patients with sickle cell disease." *Journal of Pain & Symptom Management* 47(2): 334-340.

Pain Management in Pediatrics					
Modality: Subanesthetic Ketamine					
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
<p>Journal: <i>J Pain Res</i> Author: Sheehy, K.A., et al. Year Published: 2017 Location: The Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's Research Institute, Children's National Health System, George Washington University School of Medicine and Health Sciences, Center for Neuroscience Research, Children's Research Institute, Children's National Health System, Washington, DC, USA</p>	<p>Aim: To examine the effects of subanesthetic ketamine on pain intensity and opioid intake in children, adolescents, and young adults with acute and chronic pain syndromes treated in an inpatient setting</p> <p>Study Type: Longitudinal Cohort Study</p> <p>Size: 230 different patients during 360 separate hospital admissions</p>	<p>Inclusion Criteria: Patients who received subanesthetic doses of ketamine for pain management.</p> <p>Exclusion Criteria: Patients who lacked a pain medicine consult, underwent a spinal fusion procedure (patients part of previous study), had incomplete record of pain scores and/or opioid intake, or received ketamine only for the purpose of sedation.</p>	<p>Methods: Primary outcomes from data collected included changes in pain scores and morphine-equivalent intake.</p>	<p>Results: Overall, ketamine infusions were associated with significant reductions in mean pain scores from baseline (mean pain scores 6.64 [95% CI: 6.38–6.90]) to those recorded on the day after discontinuation of ketamine (mean pain scores 4.38 [95% CI: 4.06–4.69]), $p < 0.001$. Importantly, the effect of ketamine on pain scores varied according to clinical diagnosis ($p = 0.011$), infusion duration ($p = 0.004$), and pain location ($p = 0.004$). Greater median reductions in opioid intake were observed in patients with malignancy-associated pain and patients with sickle cell disease, whereas lesser reductions were observed in patients with accidental trauma and postoperative pain after surgical trauma ($p = 0.030$ for overall difference)</p>	<p>Study Limitations:</p> <p><input checked="" type="checkbox"/> None</p> <p>Non-Randomized Studies</p> <p><input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria</p> <p><input type="checkbox"/> Flawed measurement of both exposure and outcome</p> <p><input type="checkbox"/> Failure to adequately control confounding</p> <p><input type="checkbox"/> Incomplete or inadequately short follow-up</p> <p><input type="checkbox"/> Differences in important prognostic factors at baseline</p>

Low Quality Rating if:

Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied)

Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)

Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)

Increase Quality Rating if:

Large effect

Dose-response gradient

Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

High

Moderate

Low

Very Low

References:

1. Sheehy, K. A., et al. (2017). "Subanesthetic ketamine for pain management in hospitalized children, adolescents, and young adults: a single-center cohort study." *J Pain Res* 10: 787-795.



Pain Management in Adults						
Modality: Low-dose Ketamine Infusions						
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations	
<p>Journal: <i>J Pain Palliat Care Pharmacother</i> Author: Palm, N., et al. Year Published: 2018 Location: Cleveland Clinic</p>	<p>Aim: To report a case series of five adult patients with SCD who received low-dose ketamine infusions as adjunct therapy for pain due to VOs</p> <p>Study Type: Retrospective Case Series</p> <p>Size: 5 patients</p>	<p>Inclusion Criteria: Patients were included if aged > 18 years, carried a diagnosis of sickle cell disease, and received therapy for at least 24 hours with ketamine infusion for treatment of pain while in the ICU.</p> <p>Exclusion Criteria: Patients were excluded if ketamine was administered via bolus dosing only or if it was used for a separate indication.</p>	<p>Methods: Patients with SCD with instances of ketamine infusion orders between 2010 and 2014.</p> <p>The study period included the 24 hours immediately preceding ketamine infusion therapy (day-1) through the duration of hospital stay. Data collection included patient baseline characteristics, ketamine infusion characteristics (i.e., dose and duration of therapy), and opioid use characteristics (i.e., dose in milligrams of oral morphine equivalents [MME]). Monitoring for efficacy was done by assessing daily MME before, during, and after ketamine therapy, and all documented numeric rating scale (NRS) scores. Daily MME and ketamine dosing was compared between patients and a mean calculated. For the single patient receiving methadone prior to study, methadone was converted to MME using a 12:1 conversion based on the patient's methadone total daily dose required. Safety</p>	<p>Results: During ketamine infusion, patients experienced a lower reported pain score (mean numeric rating scale [NRS] score 7.2 vs. 6.4), reduced opioid-induced adverse effects, and decreased opioid dosing requirements (median reduction of 90 mg morphine equivalents per patient). The average duration of severe pain during admission prior to ketamine therapy was 8 days.</p> <p>Only one of five patients reported an adverse effect (vivid dreams) secondary to ketamine infusion. The Richmond Agitation Sedation Scale (RASS) was assessed throughout therapy, with only one patient experiencing light drowsiness.</p>	<p>Study Limitations: <input checked="" type="checkbox"/> None Non-Randomized Studies <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline</p>	<p>Low Quality Rating if: <input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied) <input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome) <input checked="" type="checkbox"/> Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain) <input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)</p> <p>Increase Quality Rating if: <input type="checkbox"/> Large effect <input type="checkbox"/> Dose-response gradient <input type="checkbox"/> Plausible confounders or other biases increase certainty of effect</p> <p>Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very Low</p>



			was assessed using all documented Richmond Agitation Sedation Scale (RASS) scores in the electronic medical record during the study period (23). Medical charts were reviewed for any reported side effects attributable to ketamine.			
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References:

1. Palm, N., et al. (2018). "Low-Dose Ketamine Infusion for Adjunct Management during Vaso-occlusive Episodes in Adults with Sickle Cell Disease: A Case Series." *J Pain Palliat Care Pharmacother*: 1-7.

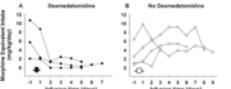
Pain Management in Adults						Low Quality Rating if: <input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied) <input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome) <input checked="" type="checkbox"/> Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain) <input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found) Increase Quality Rating if: <input type="checkbox"/> Large effect <input type="checkbox"/> Dose-response gradient
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations	
Journal: <i>Pain Research and Management</i> Author: Santos, J. et al. Year Published: 2016 Location: University of Connecticut Health Center, Farmington, CT	Aim: To evaluate the proportion of ED visits in which PCA was started in the ED Study Type: Retrospective chart review Size: 258 visits	Inclusion Criteria: Consecutive SCD pain ED visits	Methods: Collected demographics included gender, age, and race. Clinical data included hemoglobin phenotype, frequency of ED visits over the two-year period, pain scores (Numerical Rating Scale of 0-10), total number of bolus opioids administered between the time of physician decision to admit and the start of PCA, and number of bolus opioids received on the hospital floor before PCA initiation. The following specific time points were also abstracted: ED physician's decision to admit, PCA initiation time, hospital floor arrival, hospital length of stay, and last bolus opioid administration prior to	Results: 258 visits resulted in hospitalization. PCA was initiated in 230 (89%) visits of which 157 (68%) were initiated in the ED. Time to PCA initiation was longer when PCA was begun after hospitalization versus in the ED (8.6 versus 4.5 hours, $p < 0.001$). ED PCA initiation was associated with fewer opioid boluses following decision to admit and less time without analgesic treatment (all $p < 0.05$). Mean pain intensity (MPI) reduction did not differ between groups. Among visits where PCA was begun in the ED, low utilizers demonstrated greater	Study Limitations: <input type="checkbox"/> None Non-Randomized Studies <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input checked="" type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline	



			<p>PCA initiation. Abstracted time points were used to calculate the following time frames: absolute time to PCA initiation, time between last opioid in the ED and first opioid on the floor, and time to starting PCA after hospital floor arrival.</p>	<p>MPI reduction than high utilizers (2.8 versus 2.0, p = 0.04).</p> <table border="1"> <caption>Table 3. Change in ED pain score* by site of PCA initiation and visit utilizer type, mean (SD).</caption> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Visit utilizer type</th> <th rowspan="2">p-value</th> </tr> <tr> <th>High</th> <th>Low</th> </tr> </thead> <tbody> <tr> <td>PCA-ED</td> <td>2.8(1.8)</td> <td>2.0(2.2)</td> <td>0.04*</td> </tr> <tr> <td>PCA-hospital</td> <td>1.9(2.0)</td> <td>2.3(3.1)</td> <td>0.22</td> </tr> </tbody> </table> <p>*Difference in mean pain intensity between initial and final ED pain scores.</p>		Visit utilizer type		p-value	High	Low	PCA-ED	2.8(1.8)	2.0(2.2)	0.04*	PCA-hospital	1.9(2.0)	2.3(3.1)	0.22	<p><input type="checkbox"/> Plausible confounders or other biases increase certainty of effect</p> <p>Quality (certainty) of evidence for studies as a whole:</p> <p><input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very Low</p>
	Visit utilizer type		p-value																
	High	Low																	
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References:

1. Santos, J., et al. (2016). "Patient Controlled Analgesia for Adults with Sickle Cell Disease Awaiting Admission from the Emergency Department." *Pain Research and Management* 2016: 5.

Pain Management of Adults						Low Quality Rating if:
Modality: Dexmedetomidine						
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations	
<p>Journal: <i>Pain Practice</i> Author: Sheehy, K.A., et al. Year Published: 2015 Location: George Washington University School of Medicine and Health Sciences, Washington, DC</p>	<p>Aim: To evaluate the role of Dexmedetomidine in pain management during VOEs in SCD patients</p> <p>Study Type: Retrospective Case Series</p> <p>Size: 3 patients</p>	<p>Inclusion Criteria: SCD patients who had been admitted to the hospital with VOEs and had been treated with Dexmedetomidine between November 2010 and April 2014.</p>	<p>Methods: Researchers reviewed the hospital course of SCD patients who had been admitted to the hospital with VOEs and had been treated with Dexmedetomidine between November 2010 and April 2014. Records were also reviewed of SCD patients treated at the same time with similar analgesic therapy (opioids and subanesthetic doses of ketamine) who had not received dexmedetomidine. The patients treated with dexmedetomidine were identified by the authors who had cared for those patients. For the purpose of this report, high-dose opioid was defined as</p>	<p>Results: Dexmedetomidine infusions that lasted for three to six days were associated with marked reduction in daily oral morphine-equivalent intake and decreases in pain scores (numeric rating scale). There were no hemodynamic changes that required treatment with vasoactive or anticholinergic agents.</p> 	<p>Study Limitations:</p> <p><input type="checkbox"/> None</p> <p>Non-Randomized Studies</p> <p><input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria</p> <p><input type="checkbox"/> Flawed measurement of both exposure and outcome</p> <p><input checked="" type="checkbox"/> Failure to adequately control confounding</p> <p><input type="checkbox"/> Incomplete or inadequately short follow-up</p> <p><input type="checkbox"/> Differences in important prognostic factors at baseline</p>	<p><input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied)</p> <p><input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)</p> <p><input checked="" type="checkbox"/> Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)</p> <p><input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)</p> <p>Increase Quality Rating if:</p> <p><input type="checkbox"/> Large effect</p> <p><input type="checkbox"/> Dose-response gradient</p>



			those exceeding 2mg/kg/day of oral morphine-equivalent. This definition is based on a study indicating that patients requiring those doses of opioid were often treated with ketamine 19. For the present investigation the following were examined, patient demographics, SCD genotype, analgesic therapy, self-reported pain scores (numeric rating scale 0-10) and treatment related hemodynamic changes requiring intervention.			<input type="checkbox"/> Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very Low
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References:

1. Sheehy, K. A., et al. (2015). "Dexmedetomidine as an Adjuvant to Analgesic Strategy During Vaso-Occlusive Episodes in Adolescents with Sickle-Cell Disease." *Pain Practice* 15(8): E90-97.

Pain Management in Adults						Low Quality Rating if: <input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied) <input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome) <input checked="" type="checkbox"/> Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain) <input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on
Modality: Fluid replacement therapy						
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations	
Journal: <i>Cochrane Database of Systematic Reviews</i> Author: Okomo, U. and M. M. Meremikwu Year Published: 2017 Location:	Aim: To determine the optimal route, quantity and type of fluid replacement for people with sickle cell disease with acute painful crises Study Type: Systematic Review Size: 0 studies	Inclusion Criteria: Randomised and quasi-randomised controlled trials that compared the administration of supplemental fluids adjunctive to analgesics by any route in people with any type of sickle cell disease during an acute painful episode, under medical supervision (inpatient, day care or community).	Methods: Systematic Review	Results: Sixteen trials were identified by the searches, all of which were not eligible for inclusion in the review.	Study Limitations: <input type="checkbox"/> None Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality <input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies	



						<p>effectiveness of drug only small, positive studies found)</p> <p>Increase Quality Rating if:</p> <p><input type="checkbox"/> Large effect</p> <p><input type="checkbox"/> Dose-response gradient</p> <p><input type="checkbox"/> Plausible confounders or other biases increase certainty of effect</p> <p>Quality (certainty) of evidence for studies as a whole:</p> <p><input type="checkbox"/> High</p> <p><input type="checkbox"/> Moderate</p> <p><input type="checkbox"/> Low</p> <p><input checked="" type="checkbox"/> Very Low</p>
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References:

- Okomo, U. and M. M. Meremikwu (2017). "Fluid replacement therapy for acute episodes of pain in people with sickle cell disease." *Cochrane Database of Systematic Reviews* 7: Cd005406.

Pain Management in Adults					
Modality: Low-molecular-weight heparins					
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Journal: Hemoglobin Author: van Zuuren, E.J. and Z. Fedorowicz Year Published: 2014 Location: Leiden University Medical Centre, Leiden, The Netherlands and United Kingdom Cochran Centre	<p>Aim: To assess the effects of low-molecular-weight-heparins (LMWH) for managing vasoocclusive crisis (VOC) in people with sickle cell disease</p> <p>Study Type: Systematic Review</p> <p>Size: One study comprising 253 participants</p>	<p>Inclusion Criteria: RCTs in children and adults with homozygous sickle cell disease (SS) (Hb S or HBB: c.20A4T), sickle cell Hb C (HBB: c.19G4A) disease (SC), sickle cell b-thalassemia (Sb0- and Sb+-thal) (confirmed by electrophoresis and sickle solubility test, with family studies or DNA tests as appropriate) that compared any type of LMWH administered subcutaneously with</p>	<p>Methods: Systematic Review</p>	<p>Results: One study (with an overall unclear to high risk of bias) was included. This study provided limited data, but concluded that tinzaparin resulted in a more rapid resolution of pain, and in a statistically significant lower number of hospitalization days compared to a placebo. Two minor bleeding events were reported as adverse events in the tinzaparin group. Based on the results from this</p>	<p>Study Limitations:</p> <p><input type="checkbox"/> None</p> <p>Systematic Review</p> <p><input type="checkbox"/> Review did not address focused clinical question</p> <p><input type="checkbox"/> Search was not detailed or exhaustive</p> <p><input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality</p> <p><input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies</p>

Low Quality Rating if:

Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied)

Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)

Publication Bias (e.g. pharmaceutical company sponsors study on



		placebo or standard care were included.		single study, there is incomplete evidence to either support or refute the effectiveness of LMWH in people with sickle cell disease.		<p><i>effectiveness of drug only small, positive studies found)</i></p> <p>Increase Quality Rating if:</p> <p><input type="checkbox"/> Large effect</p> <p><input type="checkbox"/> Dose-response gradient</p> <p><input type="checkbox"/> Plausible confounders or other biases increase certainty of effect</p> <p>Quality (certainty) of evidence for studies as a whole:</p> <p><input type="checkbox"/> High</p> <p><input type="checkbox"/> Moderate</p> <p><input type="checkbox"/> Low</p> <p><input checked="" type="checkbox"/> Very Low</p>
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References:

1. van Zuuren, E. J. and Z. Fedorowicz (2014). "Low-molecular-weight heparins for managing vasoocclusive crises in people with sickle cell disease: a summary of a cochrane systematic review." Hemoglobin 38(3): 221-223.



Internal Policies and Protocols

Sickle Cell Suspected VOE Clinical Pathway March 2018	
Outcomes/Goals	<ol style="list-style-type: none"> 1. Create an efficient team-oriented approach in conjunction with Peds Hem/Onc (PHO service) 2. Rapid evaluation and treatment of VOE 3. Effective Pain management to a level acceptable to the patient 4. Early and efficient determination of disposition
Inclusion Criteria	<ol style="list-style-type: none"> 1. Sickle cell patients < 20 years presenting with a suspected vaso-occlusive pain event.
Exclusion Criteria	<ol style="list-style-type: none"> 1. Pts presenting with AMS, severe or atypical HA, focal neurologic findings, new seizure (consider Peds stroke pathway) 2. Pts presenting with T\geq38.0 (consider sickle cell with fever pathway)
NURSE Documentation	Document location of pain, symptoms associated with pain, quality of pain, and treatments that have worked and not worked. Document evidence of shock/decompensation, mental, respiratory and circulatory status. Document presence of fever. Document presence of central line or port and any history of line infections. Medications, allergies, vital signs and weight per Peds ED NPEOC.
INTERVENTIONS Initiate on arrival	ESI II or III Place on continuous cardiac and pulse ox monitor. Apply Oxygen for adequate oxygenation and/or patient comfort. PIV or access central line/port per CLABSI prevention Bundle policy # HC-NSG-259-POL and HC-NSG-260-PRO Consider NS fluid bolus Offer and discuss intranasal fentanyl 1.5 µg/kg x2 doses, 5-10 minutes apart (For patients \geq10 kg, max single dose 100 µg)
DIAGNOSTICS	CBC, with Diff, Reticulocyte Count, Chest X-ray, if c/o chest pain and/or SOB or demonstrating increased WOB Must obtain Chest X-ray if supplemental oxygen is indicated HCG in females \geq 12 or younger if menarche
PHYSICIAN (LIP) Documentation	Assess, document pain Recent pain medication, dose, time of last dose Allergies to any medication Order pain medication immediately (see below)
Fluids Bolus	Consider NS 20 mL/kg bolus (no proven therapeutic benefit)
Blood Products	<i>Consult Pediatric Hem/Onc prior to transfusion to determine number of units to transfuse and whether an exchange transfusion is indicated</i>
Medication Pain	IN fentanyl PO NSAID, oxycodone (mild/moderate pain) IV ketorolac, IV opioid (moderate/severe pain)
ADMISSION	Consult to Pediatric Hematology Oncology Consult PICU if Acute Chest Syndrome
*High Risk versus Low Risk Considerations	Low Risk: <ul style="list-style-type: none"> • Well-appearing with Stable vital signs • Tolerating good po • No concern for acute chest syndrome or sequestration crisis • Tolerating po pain medication • No new hypoxemia and chest x-ray without infiltrate • Reticulocyte count: • Compliant family? High Risk: <ul style="list-style-type: none"> • Toxic/ill appearing



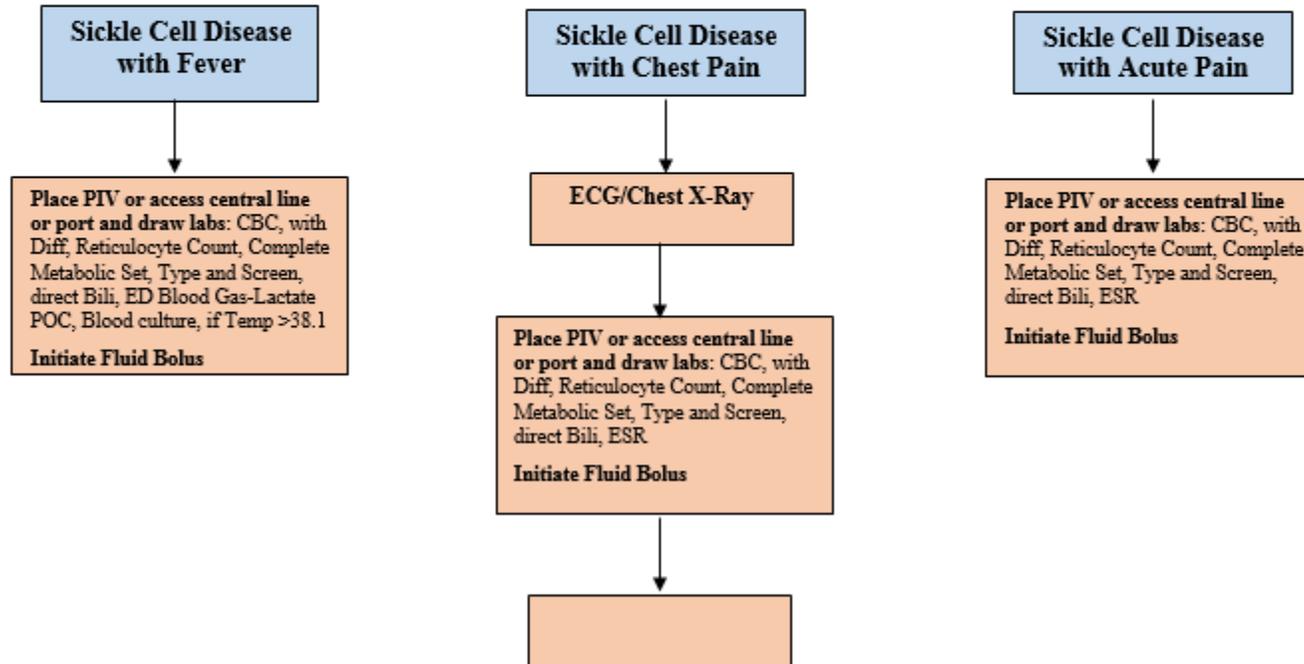
Clinical Pathway Decision Making Process

Sickle Cell

January 2017

Immediate Action

1. ESI I or II
2. Place on continuous cardiac and pulse ox monitor.
3. Apply Oxygen for adequate oxygenation and/or patient comfort.





Question 3: In people with SCD and acute chest syndrome (ACS), what is the most effective treatment to reduce mortality, resolve pain, and prevent clinical deterioration?

Guideline Recommendations

The **2014 National Heart, Lung, and Blood Institute (NHLBI)** expert panel report recommended the following for managing patients with sickle cell disease and acute chest syndrome:

1. Evaluate people with SCD who develop acute onset of lower respiratory tract diseases signs and/or symptoms (cough, shortness of breath, tachypnea, retractions, or wheezing) with or without fever for ACS. This should include a chest x-ray and measurement of oxygen saturation of pulse oximetry. **(Consensus-Panel Expertise)**
2. Hospitalize people with ACS. **(Consensus-Panel Expertise)**
3. Treat people with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, supplemental oxygen (to maintain oxygen saturation of greater than 95 percent), and close monitoring for bronchospasm, acute anemia, and hypoxemia. **(Strong Recommendation, Low-Quality Evidence)**
4. In people with SCA, give simple blood transfusion (10 mL/kg red blood cells) to improve oxygen carrying capacity to people with symptomatic ACS whose hemoglobin concentration is >1.0 g/dL below baseline. If baseline hemoglobin is 9 g/dL or higher, simple blood transfusion may not be required. **(Weak Recommendation, Low-Quality Evidence)**
5. In people with HbSC disease or HbS β -thalassemic with ACS, decisions about transfusion should be made in consultation with an SCD expert. **(Strong Recommendation, Low-Quality Evidence)**
6. In all persons with SCD, perform urgent exchange transfusion – with consultation from hematology, critical care, and/or apheresis specialists – when there is rapid progression of ACS as manifested by oxygen saturation below 90 percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion. **(Strong Recommendation, Low-Quality Evidence)**
7. Encourage use of incentive spirometry while awake. **(Strong Recommendation, Moderate-Quality Evidence)**

The **2014 National Heart, Lung, and Blood Institute (NHLBI)** expert panel report recommended the following for managing pain in patients with sickle cell anemia (SCA):

- In adults with SCA who have a history of severe and/or recurrent acute chest syndrome (ACS), treat with hydroxyurea.* **(Strong Recommendation, Moderate-Quality Evidence)**

The **2017 American College of Radiology** Appropriateness Criteria for Radiologic Management of Central Venous Access Recommended the following for device selection for patients \geq 13 years of age for the treatment of recurrent sickle cell crisis.



Variant 2. Device selection. Adult or child ≥ 13 years of age. Sickle cell anemia requires intravenous access for the treatment of recurrent sickle cell crisis.

Treatment/Procedure	Appropriateness Category
Chest port	Usually Appropriate
Arm port	May Be Appropriate
Single lumen PICC	May Be Appropriate
Double lumen PICC	May Be Appropriate
Tunneled central venous catheter	May Be Appropriate
Nontunneled central venous catheter	May Be Appropriate

PICC = peripherally inserted central catheter.

In 2015, the **American Academy of Family Physicians (AAFP)** updated the Management of Sickle Cell Disease guideline, adapted from the recommendations from the 2014 Expert Panel Report. The following recommendations were regarding acute chest syndrome:

- Treat persons with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, and supplemental oxygen (to maintain oxygen saturation > 95%), and monitor for bronchospasm, acute anemia, and hypoxemia. **(Strong Recommendation, Low-Quality Evidence)**
- Encourage use of incentive spirometry while awake. **(Strong Recommendation, Moderate-Quality Evidence)**
- Consult an SCD expert regarding transfusion in persons with HbSC or HbS β +thalassemia who have ACS. **(Strong Recommendation, Low-Quality Evidence)**
- Perform urgent exchange transfusion in consultation with hematology, critical care, and/or apheresis subspecialists when there is rapid progression of ACS as manifested by oxygen saturation below 90% despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion. **(Strong Recommendation, Low-Quality Evidence)**
- Give simple blood transfusion (10 mL of red blood cells per kg) to improve oxygen-carrying capacity in persons with sickle cell anemia who have symptomatic ACS and whose hemoglobin concentration is > 1.0 g per dL (10 g per L) below baseline. If baseline hemoglobin is ≥ 9.0 g per dL (90 g per L), simple blood transfusion may not be required. **(Weak Recommendation, Low-Quality Evidence)**

The **2000 American Academy of Family Physicians (AAFP)** recommended the following:

- Primary care management
 - o Respiratory symptoms with essentially normal oxygen saturation and negative chest radiography: liberal administration of oxygen, incentive spirometer, bronchodilators
- Consultation recommended
 - o Low oxygen saturation
 - o Abnormal findings on the chest radiography
 - o Dyspnea



References:

1. Expert Panel Report. Evidence-based management of sickle cell disease. In: U.S. Department of Health and Human Services. Bethesda, MD: National Heart, Lung, and Blood Institute; 2014.
2. Wethers, D. L. (2000). Sickle cell disease in childhood: Part I. Laboratory diagnosis, pathophysiology and health maintenance. *American Family Physician*, 62(5), 1013-1020, 1027-1018.
3. Yawn, B. P., & John-Sowah, J. (2015). Management of Sickle Cell Disease: Recommendations from the 2014 Expert Panel Report. *American Family Physician*, 92(12), 1069-1076.

Health System Guidelines

In 2012, **Seattle Children's Hospital** released the Sickle Cell Disease Critical Elements of Care Guideline

- 5-Month Check by Comprehensive Program/Teaching Goals for Age
 - Acute chest syndrome: Discuss how respiratory distress or chest pain may signal problems and call for immediate medical evaluation. Normally, chest x-ray, CBC, retic and oximetry would be done. Antibiotics and oxygen should be administered, and transfusion may be provided in acute chest syndrome. Consider including antibiotic coverage for chlamydia and mycoplasma infection. Discuss the importance of expanding lungs to avoid atelectasis and recruit collapsed regions of lung. This is done with age-appropriate approaches.
- 2 1/2-Year Check by Comprehensive/Primary Care Program/Teaching Goals for Age (Annually on the half year)
 - Introduce concepts of incentive spirometry for lung expansion when sick or during pain episodes. Discuss age appropriate substitutes for incentive spirometry.
- 5 ½- and 6 ½- Year Check by Comprehensive Program/Teaching Goals for Age
 - Reinforce incentive spirometry during pain episodes and illness to prevent acute chest syndrome

General Principles of Pain Management: a number of general principles can be applied to the management of pain in sickle cell disease

- Access often for respiratory compromise, as hypoxemia may contribute to episodes of acute chest syndrome. Incentive spirometry while on opiates.



Acute Chest Syndrome

Diagnosis	Monitoring	Diagnostic (if not previously obtained)	Fluids, Nutrition, General Care	Medications/ Treatments	Discharge Criteria
<p>Definition: A new infiltrate on CXR in a patient with sickle cell disease.</p>	<ol style="list-style-type: none"> Vital signs q 2-4 hr. Continuous pulse oximetry. Consider CR monitor. Record I + O, daily weight 	<ol style="list-style-type: none"> CBC, diff., platelet count and reticulocyte count initially and daily until improving (compare with patient's baseline values). CXR. Repeat for clinical deterioration looking for progression. May need serial CXRs. Type and cross match (minor-antigen-matched if available, sickle negative, leukocyte depleted RBC) to have blood available. Obtain red cell extended phenotyping for sickle cell patients if not done previously (at a minimum type for RhD, Cc, Ee and Kell). Blood cultures if T > 38.2°C or history of recent fever. Capillary or arterial blood gas and assessment by PICU team for severe illness. 	<ol style="list-style-type: none"> Maintain "euvoemia." IV + PO 1-1.25 x maintenance. More fluid is appropriate only if patient is dehydrated or if insensible losses are increased (e.g. persistent fever). Incentive spirometry x 10 breaths q 2 hr. during the day (0800-2200), if awake at night, and prior to all CXRs. Encourage ambulation, activity. 	<ol style="list-style-type: none"> Oxygen to maintain O₂ saturation > 93% Ceftriaxone 75mg/kg Q 24 hr. IV. (Prophylactic penicillin may be discontinued while on broad-spectrum antibiotics.) Azithromycin 10mg/kg PO x1, then 5 mg/kg PO QD days 2-5, or other macrolide antibiotic. Chest physical therapy if consolidation is present. Follow patients specific pain plan. If not available consider morphine 0.1 mg/kg IV q 2 hr. or 0.01 - 0.1 mg/kg/hr. continuous infusion or PCA for severe pain. Alternative analgesics (but not demerol) may be used in individual cases. Adequate pain relief is essential to avoid splinting improve respiratory dynamics that worsens respiratory status. Consider round the clock bronchodilators, especially if patient has history of wheezing or asthma. Some patients benefit even if not clinically obstructed. Consider use of BiPAP or CPAP if not improving with routine measures. Consider red cell transfusion for progressive respiratory decline despite incentive spirometry and #1-6 above. Pain control and incentive spirometry are commonly under-utilized. Transfuse initially if severely ill. <ol style="list-style-type: none"> Simple transfusion to a Hct of 30% (no clear benefit to exchange transfusion). Exchange transfusion for patients with progressive disease and a Hct > 27% or lack of improvement > 36 hrs post simple transfusion. Target a Hct of 30% and Hb S or Hb S + C < 30 %. (May require transfer to ICU for erythrocytapheresis). Remove femoral or central venous catheters as soon as possible after exchange transfusion to reduce risk of thrombosis. See other Clinical Care Paths for acute anemic crisis, stroke, priapism, if present. Continue prophylactic folic acid, if applicable. 	<ol style="list-style-type: none"> Off O₂. Afebrile > 24 hr and negative cultures for 24 hours (if applicable). Good oral intake, able to take all oral medications including antibiotics. Adequate pain relief (if needed) with oral analgesics. Discharge instruction completed regarding home use of incentive spirometry while on opiates. Follow-up plans coordinated with hematology service. CXR to establish new baseline in 2-3 months.



Primary Literature:

NHLBI Systematic Review: Summary of the Evidence

One RCT, 27 observational studies, and 45 case reports described sickle cell-related ACS. The overall quality of evidence was very low for all interventions except the use of opioids.

The single RCT enrolled 38 children and found that **dexamethasone compared to placebo decreased the mean hospital stay (from 80 to 47 hours), the need for transfusions (from 47 percent to 9 percent), the number of administered opioid doses (from a mean of 20 to a mean of 2.5), and clinical deterioration (defined as an increase in oxygen requirements and respiratory rate).** Participants and investigators were blinded, allocation was concealed, and the study did not report any baseline imbalances. This short-term benefit, however, was not demonstrated to persist when examined by larger observational studies with longer follow-up. The largest of these studies was done in 2009 and retrospectively evaluated more than 3,000 people (more than 5,000 admissions). After adjustment for propensity scores and hospital case mix, **the study demonstrated a significant increase in the length of hospitalization in people who received corticosteroids as part of their ACS management. Other studies showed increased adverse effects related to steroids.**

The remaining observational studies described benefits of other therapies for ACS (e.g., supportive treatment including oxygen supplementation, mechanical ventilation, pain management, hydration, antibiotics, and simple or exchange transfusion). The quality of these studies was low due to the noncomparative nature of their design. Studies that evaluated antibiotics did not demonstrate a significant effect on patient-important outcomes. Multiple observational studies evaluated opiates in ACS. In one, nalbuphine hydrochloride reduced the incidence of ACS compared to morphine (12 percent vs. 29 percent) and also reduced hospital stay. In the remaining studies, **opiates clearly reduced pain but without other effects on the clinical course of ACS. Transfusion studies in ACS showed conflicting results.** In one study, length of hospital stay was similar between simple transfusion and exchange transfusion, and ICU stay was longer in the exchange group (5.6 days vs. 2.6 days). Another study found significant correlation between exchange transfusion and fewer days of hospitalization and oxygen requirement. In these and other transfusion studies, sicker patients were more likely to receive exchange transfusion, which indicates a clear selection bias.

References:

1. Expert Panel Report. Evidence-based management of sickle cell disease. In: U.S. Department of Health and Human Services. Bethesda, MD: National Heart, Lung, and Blood Institute; 2014.



Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high
Observational study–low
Any other evidence–very low

Criteria for increasing or decreasing level

Reductions
Study quality has serious (–1) or very serious (–2) problems
Important inconsistency in evidence (–1)
Directness is somewhat (–1) or seriously (–2) uncertain
Sparse or imprecise data (–1)
Reporting bias highly probable (–1)
Increases
Evidence of association† strong (+1) or very strong (+2)
Dose-response gradient evident (+1)
All plausible confounders would reduce the effect (+1)



†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.



Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania’s Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine’s “Standards for Developing Trustworthy Clinical Practice Guidelines” (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:

Who wrote the initial draft

How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest



A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
 Describe itself as systematic or report search strategies using multiple databases



Define the scope of the review (including key questions and the applicable population)

Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.



7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.