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Outpatient and Inpatient Management of Acute Sickle Cell Disease Pain

Mica Ferlis, MSN, RN, ACNP-BC Virginia Commonwealth University " '10' Redefined" Hertz Nazaire 1973-2021



Acute SCD Pain Definition

- Lasts at least 2 hours
- Started in last 10 days
- One physical sign (palpation, movement causes pain, or decreased ROM)
- Can't be explained by SCD complication (leg ulcer, priapism, edema, bone infarction, AVN, osteomyelitis, and hepatobiliary)
- Subtypes
 - 1-No painful comorbidity
 - 2-With painful comorbidity
- May occur with or without chronic SCD pain

ROM, range of motion; AVN, avascular necrosis. Field JJ et al. *J Pain*. 2019;20(7):746-759.



Chronic SCD Pain Definition

- Pain on most days over the past 6 months
- One sign of pain sensitivity (movement, palp., etc)
- Three diagnostic modifications allowable
 - Chronic SCD pain without contributory disease complications--likely nociplastic (formerly called centralized)
 - Chronic SCD pain with contributory disease complications
 - Chronic SCD pain with mixed pain types
- Often acute-on-chronic pain (mixed pain types)

Dampier C et al. J Pain. 2017;18(5):490-498.



Chronic Nociplastic (Formerly Centralized) Pain

SCD Frequency of Descriptors, with QST Classification

139 (78)

7(4)

31 (17)

17 (10)

14 (9)

3 (2)

23 (13)

23 (13)

12(7)

10(6)

35 (20)

24 (13)

29 (16)

33 (18)

51 (29)

18 (10)

10 (6)

39 (22)

5(3)

10 (6)

86 (48)

52 (29)

83 (46)

23 (13)

63 (35)

39 (22)

3 (2)

2(1)

Aching

Boring

Burning

Cold

Cool

Drawing

Drilling

Flashing

Flickering

Freezing

Hot

Itchy

Jumping

Numb

Lancinating

Penetrating

Pricking

Quivering

Radiating

Scalding

Searing

Shooting

Smarting

Stabbing

Stinging

Tingling

Tight

Spreading

Selected Word Overall (n=179) Central (33, 18%) Mixed (23, 13%) Norma

19 (58)

3 (9)

8 (24)

7 (21)

5(15)

6(18)

3 (9)

1(3)

2 (6)

6(18)

6(18)

6(18)

1 (3)

8 (24)

9 (27)

4(12)

1(3)

6(18)

2 (6)

3 (9)

11 (33)

0 (0)

15 (46)

17 (56)

7 (22)

14 (42)

10 (30)

1(3)

20 (87)

1(4)

5 (22)

4 (17)

2 (9)

0(0)

3 (13)

5 (22)

0 (0)

3 (13)

6 (26)

3 (13)

5 (22)

0 (0)

3 (13)

9 (39)

4(17)

1 (4)

7 (30)

1(4)

2 (9)

0 (0)

15 (65)

10 (44)

12 (52)

5 (23)

6 (26)

4(17)

•	After	nerve	injury
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- Maladaptive changes •
- Pos/neg signal rebalancing ٠
- Along the entire nociceptive pathway within the CNS
- Spontaneous pain
- Pain hypersensitivity
- Different pain descriptors used
- Sxs vary enormously across • individuals according to:
 - Etiology
 - Genotypical factors
 - Environmental factors _

von Hehn CA et al. Neuron. 2012;73(4):638-52. Wilkie DJ et al. J Natl Med Assoc. 2010;102(1):18-27. Dyal BW et al. Nurs Res. 2019;68(5):365-373.



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Etiologic Classification of SCD Pain

Acute pain syndromes

Vaso-occlusive crisis Acute chest syndrome Acute abdominal syndromes Cholelithiasis/Choledocholithiasis Acute cholecystitis Acute hepatic sequestration Hepatic crisis Acute intrahepatic cholestasis Splenic sequestration/infarction Bowel ischemia Medullary infarction/papillary necrosis Priapism Dactylitis

TIA, transient ischemic attack



Neuropathic (but not <u>central) pain syndromes</u>

Mental nerve neuropathy Ischemic optic neuropathy Spinal cord infarction TIA/stroke

Chronic pain syndromes

Avascular necrosis Arthropathies Vertebral body collapse Leg ulcers Cholelithiasis/Choledocholithiasis Nociplastic (formerly centralized) pain

Precipitating Factors for VOC

- Infection
- Dehydration
- Cold temperature
 - Weather; air conditioning; swimming in cold water
- Windy weather and low humidity
- Climate and geography

 - Higher monthly temperatures: ↓ pain and frequency

- Metabolic acidosis
- Menstruation
- Pregnancy and postpartum
- Emotional stress
- Physical stress
- Sleep apnea

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



Provider Misperceptions

- Many studies: provider attitudes, misperceptions interfere with assessment of pain, lead to undertreatment
- 86% of academic hospitalists do not believe that self report is the most reliable indicator of pain in SCD patients
- Survey of ED physicians, hematologists, 53% and 23% thought > 20% of SCD patients are addicted to opioids
- Survey of 77 nurses who treat SCD, 63% believed addiction develops frequently

These misperceptions must be addressed to provide optimal care for SCD patients

Labbé E et al. *J Palliat Care*. 2005;21:246-251. Shapiro BS et al. *J Pain Symptom Manage*. 1997;14:168-174. Pack-Mabien A et al. *Appl Nurs Res*. 2001; 14:187-192.



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Opioid Use Disorder

- Prevalence of opioid use disorders in SCD
 - Similar or lower than general population
 - Greatly overestimated by clinicians
 - NOT THE SAME as tolerance or physical dependence
- The following do NOT suggest an opioid use disorder
 - Large doses or frequent administration of opioids under medical supervision
 - Increased dosing requirements due to tolerance
 - Withdrawal when opioids are discontinued







Challenges in Managing Pain in Sickle Cell Patients

- Ischemia from vaso-occlusion lacks clinical correlates
 - Physical exam
 - Lab work
 - Imaging
- Evidence weak for treating acute pain either in the hospital or at home
- Incongruent or absent pain behaviors exhibited by many patients
- Bad or negative experiences with previous patients
- Pain is poorly characterized
- Maladaptive coping skills
- Under treatment of mental illness

Smith WR et al. J Natl Med Assoc. 2005;97(2):183-93.



Home Care for VOC

- Most frequent setting for acute and chronic management of pain
- Patients should have an individualized plan that includes:
 - Escalation of treatment
 - Use of long and short acting opioids
 - Adjunctive therapies-heat, hydration, rest, relaxation, visualization, etc
 - Instructions for when to seek medical care





Assessing a Pain Episode

- Gold standard for assessing a patient's pain is their (or their family's) report
- The cornerstone for evaluation of a pain episode in a SCD patient is trust between the treating provider and the patient
- No clinical or lab findings exist to determine or confirm whether an individual with SCD is in pain
 - The absence of hemolysis or presence of stable Hgb should NOT be used as a reason to withhold medication or decrease the dose of medication
- Failure to appropriately and quickly assess the intensity and cause of pain may lead to delay in opioid analgesia which may worsen pain and coping mechanisms

Yawn BP et al. *JAMA*. 2014;312:1033-1048. American Pain Society. Guideline for the management of acute and chronic pain in sickle cell disease. 1999.



Triage Process

RN/APP calls (or get called by) patient-assess symptoms to see if IC or ED more appropriate

- Pain location/severity/duration/exacerbating and relieving factors; typical or atypical for VOC?
- If extremity pain, laterality/swelling, acute/chronic?
- Fever, new CP/SOB/cough, new/worse fatigue; infection risk (COVID/flu)?
- What have you done so far at home/last dose(s)?
- Ride status
- Do you think you need to be admitted?
- Are you out of home medications/adjuncts?

VOC, vaso-occlusive crisis.

Lanzkron S et al. Ann Intern Med. 2021;174(9):1207-1213. Erratum in: Ann Intern Med. 2021; PMID: 34224261.



Pain Assessment Includes:

- Location
- Severity
- Duration
- Potential exacerbating factors
- Typical versus atypical pain
- Differentiate vaso-occlusive pain from somatic and/or visceral pain



Guidelines for Treating Acute SCD Pain NHLBI Expert Consensus Panel, 2014

- Eligible Studies reviewed
 - 32 RCTs with more than 1,800 people of all ages
 - 34 observational studies
 - 30 case reports
- Highest quality evidence, strongest recommendation for <u>opioids within 30-60</u> <u>minutes of arrival in the Emergency Department</u>
 - Evidence from several RCTs and observational studies supports opioids for VOCs
 - Indirect, high-quality evidence from populations without SCD also supports opioids for VOCs
- RCTs and observational studies support NSAIDs, were conflicting, but reduced pain decreased LOS
- Several RCTs and observational studies support the use of <u>around-the-clock dosing</u> vs intermittent for VOCs

National Institutes of Health. U.S. Department of Health and Human Services. Evidence-based Management of Sickle Cell Disease. Expert Panel Report. 2014 Yawn BP et al. JAMA. 2014;312(10):1033-1048. Erratum in: JAMA. 2015;313(7):729. JAMA. 2014;312(18):1932.



Guidelines for Treating Acute SCD Pain: ASH 2020

Recommendation	Strength			
Tailored opioid dosing	Conditional			
NSAIDs in addition to opioids	Conditional			
Corticosteroids	Against			
Analgesic ketamine infusion adjunct to opioids	Conditional			
Regional anesthesia for localized refractory pain	Conditional			
IV fluids plus standard pharm's	No recommendation			
Massage, yoga, TENS, VR, guided relax + pharm	Conditional			
Acupuncture, biofeedback	No recommendation			
SCD-specific day hospital, infusion centers vs ED	Conditional			
Basal + on-demand/scheduled intermittent opioid	No recommendation			

TENS, transcutaneous electrical nerve stimulation; VR, virtual reality. Brandow AM et al. Blood Adv. 2020;4(12):2656-2701.



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Superiority of IC Over ED Care for SCD Pain

- Mean time to 1st dose = 62 min IC vs 132 min in ED
- Probability pain reassessed within 30 min of first dose 3.8x greater in IC than ED
- Probability of admission to IC << ED by factor of 4

Lanzkron S et al. Ann Intern Med. 2021;174(9):1207-1213. Erratum in: Ann Intern Med. 2021 Aug 3.



Summary: Acute Pain Management in ED or IC

- Prompt administration of pain management

 Ideally within 30 min
- Frequent reassessment (every 20-30 minutes)
- If pain not controlled after 2 doses (usually 3-4 at VCUHS) rounds of IV opioid analgesia, hospitalization is sometimes recommended
- Use of ineffective therapies (placebo) should NEVER be used
- Varying perspective on use of NSAIDs
 - Ketorolac often used but some feel benefits do not outweigh risks



Derived from American Pain Society, NHLBI Consensus 2014, ASH Guidelines 2020









Acute Pain Management as an Inpatient

- Patient Controlled Analgesia (PCA)
 - Provides most even therapy and allows for self-administration
 - Dose is determined by ED usage and previous inpatient stays
 - Several ways to dose PCA
 - > At VCUHS, no basal rate is given for adult SC patients
 - Patient takes oral long-acting opioid from home regimen and usually some variation of home short acting
 - Demand dosing is every 6-10 minutes depending on agent use
 - <u>VCUHS DOES NOT USE a clinician bolus</u> \rightarrow <u>TOTP</u>
- Must treat breakthrough pain
 - Swift increase in pain while a patient is being treated with continuous or around the clock opioids

TOTP, tiered oral therapy protocol



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Acute Management as an Inpatient

- IV not necessary unless dehydration or AKI (with dextrose if continuous)
- Hydroxyurea-continue it (few reasons to hold)
- Supplemental O₂ if sat < 90%
- **Objective** pain and functional assessment
- Assess sedation
- Orders with triggers to temporarily hold opioids PRN
- Bowel regimen
- Rx nausea and pruritis; avoid IV benadryl (个 central opioid effects)
- VTE Prophylaxis

AKI, acute kidney injury; VTE, venous thromboembolism.



Adjunctive Support

- Heat
- Insomnia treatment
- Psychosocial support
- Gentle massage
- Treatment of neuropathic pain

Yawn BP et al. *JAMA*. 2014;312:1033-1048. Mann-Jiles V et al. *J Am Assoc Nurse Pract*. 2015:27:441-449.





Weaning Opioids and Discharge

- Avoid weaning in the first 24-36 hours
- Wean incrementally (~25% of the dose every 12-24 hours)
- Decrease the dose rather than increase the interval
- Convert to oral pain regimen when the IV dose is roughly equivalent; TOTP does not convert but equal dosing achieved as oral doses are continued
- Wait several hours after initiating PO pain regimen before discharge to ensure pain is adequately managed
- Ensure patient has PO medications available prior to discharge

Chou R et al. Ann Intern Med. 2015:162:276-286.



Sickle Cell Treatment Plans

- Example resource for inpatient management of **<u>our</u>** clinic patients
- Individualized plan
- Provide starting PCA dose and TOTP
- Any patient-specific recommendations



Treatment Plan Example-ED

• ED/SCIC Pain Management Plan:

On arrival, administer IV hydromorphone 4 mg.

On arrival, administer concurrent dose of PO oxycodone 30 mg

*** consider dose reducing opiates by 50% and space dosing out to 60-120 minutes if GFR < 30 for ALL subsequent PO and IVP doses***

Reassess in 30-60 minutes. If pain is improving, continue same IV dose for subsequent doses. If pain is still intolerable or original dose did not help, can increase subsequent IV dose(s) by 25-50% (can use 5-6mg IVP for subsequent IVP doses). IVP doses can be given every 30-60 minutes if patient is not over-sedated and no other clinical concerns warranting further provider titration or dose modification.

Give max of 3-4 doses IV hydromorphone before assessing for final disposition. Monitor for OVER-sedation.

May repeat PO IR oxycodone 30 mg ONCE three hours after initial oral dose. Monitor for OVER-sedation.

Start Ketorolac 30 mg IVP Q6H unless otherwise contraindicated (AKI, bleeding, gastritis, etc)

Avoid IV diphenhydramine; can use PO diphenhydramine, hydroxyzine and/or famotidine for side effects from opiates if needed.

PO hydration only unless appears dehydrated or labs suggest dehydration – consider isotonic maintenance fluids over boluses.

Please do not discharge w/ opiate or benzo prescriptions w/out consultation from SC team.

Opioid Conversions for IV hydromorphone 4mg

- = 20 mg IV Morphine
- = 200 mcg Fentanyl

Is this patient a part of the Tiered Oral Therapy Protocol: YES

Highest demand dosing from last admission

 IV hydromorphone PCA 2 mg Q10 minutes with no CB

Outpatient Pain Regimen:

- IR oxycodone 30 mg Q3-4H PRN
- Fentanyl patch 75 mcg Q72H basal
- Ibuprofen 600 mg TID PRN



Inpatient

Inpatient Pain Management Recommendations:

Start PCA of IV hydromorphone 1 mg every 10 minutes. Assess for adequate analgesia every 4 hours; titrate by 25-50% until adequate analgesia achieved.

Monitor for OVER-sedation.

No clinician bolus

Continue Fentanyl patch 75 mcg Q72H for basal pain control Dosing based on TOTP guidelines:

Phases 1-2

Moderate pain: IR oxycodone 30 mg every 4 hours PRN Severe pain: IR oxycodone 60 mg every 4 hours PRN

Phases 3-4

Scheduled IR oxycodone 30 mg every 4 hours

Moderate pain: IR oxycodone 15 mg every 4 hours PRN

Severe pain: IR oxycodone 30 mg every 4 hours PRN

Please do not discharge with opiate or benzo prescriptions without consultation from SC team.

Adjuncts

Adjuncts:

IV ketorolac 30mg Q6H x48H followed by scheduled ibuprofen 600 mg TID as long as renal fxn intact Lidocaine patches Capsaicin gel Heating pads/warm compresses

Normal Lab Values:

Normal Hgb range: 10-13 g/dL Transfusion criteria: < 7 g/dL Transfusion schedule: no Normal Retic range: 1.5-5% Normal WBC range: 4-12 10e9/L

General Guidelines for all Sickle Cell Patients:

Incentive Spirometry- 10 breaths every hour while awake

Avoid IV diphenhydramine; can use PO diphenhydramine, hydroxyzine and/or famotidine for opiate side effects if needed. If patient cannot take PO, consider provider titrated low dose (0.01 mg/mL) naloxone gtt.

PO hydration only unless appears dehydrated or labs suggest dehydration – consider isotonic maintenance fluids over boluses.



Adjustment of Opioid Doses for CKD

		Time from arrival (min)								
Medication	Route	Arrival			30	60	90	120	150	180
Hydromorphone	IV	1 mg	GFR	GFR >30	1-3mg	1-3 mg				
				GFR <30		0.5-1.5 mg		0.5-1.5 mg		
Morphine	РО	30 mg		GFR >30						30 mg
				GFR <30						*NO*
Ketorolac	IV		Check	GFR >30	30 mg					
				GFR <30	*NO*					

CKD, chronic kidney disease.



Tiered Oral Therapy Protocol (TOTP) for Sickle Cell Vaso-occlusive Crisis Please consult Sickle Cell Clinical Team (pager 9800) for opioid-naïve patients Opioid-tolerance is defined as patients receiving for one week or longer: oral morphine 60 mg/day oral oxycodone 30 mg/day oral hydromorphone 8 mg/day transdermal fentanyl patch 25 mcg/hour or an equianalgesic dose of another opioid Phase 3 (36hr) Phase 1 (0-36hr) Phase 2 (24hr) Phase 4 TAPER DOWN TITRATE UP **OBSERVE** PLACEMENT Basal Basal Basal Continue home long-acting PO Continue home long-acting PO Continue home long-acting PO regimen regimen regimen *only if receiving basal therapy at home PCA Decrease PCA by 25% of maximum Phase 2 dose every 12 PCA PCA hours until PCA off *Will require 3 PCA dose reductions Start PCA demand dose only Continue current PCA settings based on Sickle Cell Treatment x24 hours Plan once adequate analgesia has **Oral Breakthrough** been achieved Up-titrate demand dose by 25-Decrease PO PRNs Discharge 50% every 2-4 hours as needed PRN Moderate pain: for pain 0.5x home immediate release before noon dose every 3 or 4 hours PRN Severe pain: **Oral Breakthrough Oral Breakthrough** 1x home immediate release Start PO PRNs Continue PO PRNs for dose every 3 or 4 hours Moderate or Severe pain PRN Moderate pain: 1x home immediate release **Oral Scheduled** dose every 3 or 4 hours Schedule 1x home immediate release regimen PRN Severe pain: 2x home immediate release Add comments to "Special dose every 3 or 4 hours Instructions Type-in" section

for nurses (see back)

Abbreviation key: PO: oral, PCA: patient controlled analgesia, PRN: as needed, LOS: length of stay

Created by Margaret Guy MD, Lauren Cherry Magee PharmD, and DaleMarie Vaughan PharmD. Approved by Inpatient Sickle Cell Committee. Last edited 12/09/19.

References: CDC Guideline for Prescribing Opioids for Chronic Pain. MMWR 2016 • Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy. US DHHS, FDA 2015

Continued on back

Phase 1 - Day of rest and recovery

- Goal is to reach adequate analgesic dose within first 24-36 hours
- If pain is not adequately controlled titrate PCA dose only (increase by 25-50%). Oral breakthrough dose should remain stable
- Monitor for oversedation
- Consider <u>scheduled</u> ketorolac x48 hours followed by scheduled oral NSAID unless contraindications exist (CKD, papillary necrosis, allergies)
- Consider adjunctive pain management: lidocaine patches, diclofenac gel, capsaicin cream

Phase 2 - Hold Steady

- This 24 hour period begins when the patient has reached an appropriate level of analgesia.
- No escalation or weaning of PCA for 24 hours (leave regimen the same)

Phase 3 – Initiate Weaning of PCA

- Schedule home oral immediate release with additional oral tiered therapy based on pain score
 - PRN and scheduled medication should have the same dosing interval (every 3 or 4 hours)
 - Tiered PRNs should be administered at the same time as the scheduled dose
 - Only one PRN dose can be administered per time period. If the patient receives the dose for moderate pain they can next receive a dose of pain medication at the time of their next scheduled dose.
 - Add comments to "Special Instructions Type-in" section of medication orders:

For PRN orders:

PRN Moderate pain: "Only administer one PRN per time interval. Cannot administer severe pain PRN until <u>X</u> hours have passed" For Scheduled orders: "Patient may refuse. Hold for sedation."

- · Begin weaning PCA by 25% after oral dose has been scheduled
- Begin preparing for discharge Does the patient have follow-up appointment and pain medications at home? Team to contact pager 9800 regarding anticipated discharge

Phase 4 – Day of Discharge



Phase 3 Oral Regimen Example

If home regimen is X mg every 3 hours PRN:

Schedule X mg every 3 hours with parameters "hold for patient refusal or sedation"

Order Additional PRN Doses:

- 0.5X mg (1/2 home dose) every 3 hours PRN moderate pain
- X mg (home dose) every 3 hours PRN severe pain

Total Dose Received:

Mild Pain Score = X mg every 3 hours

Moderate Pain Score = 1.5X mg every 3 hours

Severe Pain Score = 2X mg every 3 hours

Pearls:

- If a patient has two home PRN oral narcotics choose the medication listed for moderate pain as patient's home immediate release regimen
 - Example: oxycodone 10 mg PO PRN moderate pain and hydromorphone 4 mg PO PRN severe pain
 - Use: oxycodone 10 mg
- If a patient takes 1-2 tabs of a medication PRN choose the lower dose as patient's home immediate release regimen
 - Example: oxycodone 10 mg, take 1-2 tablets every 4 hours PRN
 - Use: oxycodone 10 mg
- Base initial therapy off of written prescriptions but if there is a discrepancy in what is written and what is taken by the patient please notify sickle cell clinical team (Pager 9800)
- · Avoid escalation of PO regimen while receiving PCA
- If pain appears out of proportion to exam consider sequelae of SCD including AVN and consider follow-up imaging or laboratory testing
- Involve sickle cell clinical team if any clinical concerns exist difficult titration/poor analgesic response, clinical decompensation (acute chest, AVN, etc.) (Pager 9800)

Other Pain Control Options:

- Lidocaine gtt
- Dexmedetomidine gtt •
- Ketamine gtt or IVP



Must Adopt an Institutional Approach to Pain

Clinicians

- Conflicting attitudes about care
- Patient/clinician trust and/or conflicts
- Undertreating pain
 - Pain management knowledge
 - Opiate use preconceptions/misconceptions

Patients

- Distrust for health care systems
- Distrust of clinicians
- Pain disorders
- Opiate misuse or opiate use disorder
- Mental health needs and chemical coping



Find Another Sickle Cell Champion(s)

- An inpatient, outpatient, and/or emergency department provider who wants to provide best care for SCD
- Organize an <u>institutional approach</u> to SCD pain
- <u>Meet often</u> and discuss efficacy and next steps
- LEAD by example-designate an SCD provider to round if possible, provide continuity/consistency and gain patient trust







Lead By Example

- Patience–It takes time to change patient, provider, institutional behavior – trust the process
- Consistency/Persistence
- **Advocacy**—within limits of patient needs, institutional pain guidelines
- **Organization**–define your role
 - Are you consulting or primary?
 - Placing orders or other?

- Diffusion of Innovation (Everett Rogers)
- Tipping Point (Malcom Gladwell)



Adoption Time

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Questions?



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