Texas Children's Hospital

DATE: July 2017

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Sickle Cell Disease in Vaso-Occlusive Crisis
Evidence-Based Guideline

Definition: Sickle cell disease is an inherited red blood cell disorder that can cause both acute and chronic complications and is used to refer to the many genotypes that cause the characteristic clinical syndrome. (1)

Pathophysiology: Sickle cell anemia (otherwise known as HbSS, or homozygous β^s allele) is the most common form, with the second most prevalent type being HbSC, or HbS/β-thalassemia. (1) The genetic mutation that causes sickle cell disease creates an HbS polymerization that can disrupt hemoglobin architecture and flexibility and oxidative cellular stress. (1) The mutation can result in the processes of vaso-occlusion with ischemia and reperfusion injury and hemolytic anemia. (1)

Epidemiology: It is estimated that sickle cell disease affects approximately 100,000 Americans in the United States, and occurs in 1 of every 365 Black or African American births, and 1 of every 16,300 Hispanic-American births. Approximately 1 in 13 African-American babies is born with sickle-cell trait. With the utilization of pneumococcal vaccines and hydroxyurea therapy, the mortality rate for sickle cell disease has been dramatically reduced. (2)

Etiology: Vaso-occlusion crises (VOCs) are thought to be caused by microvascular obstruction and tissue ischemia (ischemia-reperfusion injury) and hemolytic anemia. (1) Although VOCs commonly occur in the extremities, when they occur in other sites they may be confused with, or can be in the early stages of, other acute complications, and etiology of the pain must be determined in order to rule out potential causes other than uncomplicated VOC. (3) Other acute complications that can manifest in acute vaso-occlusive pain include stroke, acute chest syndrome, renal infarction, myocardial infarction, priapism, splenic or hepatic sequestration. (3)

Acute chest syndrome (ACS) is both a common and serious complication of sickle cell disease. Symptoms of lower respiratory tract disease can present suddenly and be accompanied by a new pulmonary infiltrate on chest x-ray, although these changes may be subtle in the early stages. (3) The most common well-defined etiology is viral or bacterial infection (particularly *Mycoplasma pneumoniae*), but the complication may also result from bone marrow fat embolism, intrapulmonary aggregates of sickled cells, atelectasis, or pulmonary edema. (3)

Inclusion Criteria
- Patients 1-21 years with sickle cell disease

Exclusion Criteria
- Children <1 year
- Patients without sickle cell disease
- Patients who exhibit signs of stroke

Diagnostic Evaluation
History: Assess for
- Lower respiratory symptoms (cough, wheezing, tachypnea, chest pain) and/or
- Previous history of acute chest syndrome episode, asthma, or stroke/transient ischemic attack
- Vaccination status

Physical Examination
- Assessment for the possibility of other serious complications concurrently with the treatment of pain
- Assess for abnormal vital signs, particularly changes in respiratory rate (RR), use of accessory muscles, color
- Auscultate lungs
- Assess for pain associated with abdominal distension for hepatic or splenic sequestration or acute cholecystitis, jaundice, or hematuria,
- Obtain pulse oximetry; detect new onset hypoxemia
- Rate severity of SCD according to Clinical Respiratory Score (CRS) (See Table 1)
- Evaluate for signs and symptoms of shock (See Table 2 and 3)

Table 1. Clinical Respiratory Score

Clinical Respiratory Score (CRS)			
Assess	**Score 0**	**Score 1**	**Score 2**
Respiratory Rate	<2 mos: <50 2-12 mos: <40 1-5 yrs: <30 >5 yrs: <20	<2 mos: 50-60 2-12 mos: 40-50 >1-5 yrs: 30-40 >5 yrs: 20-30	<2 mos: >60 2-12 mos: >50 >1-5 yrs: >40 >5 yrs: >30
Auscultation	Good air movement, scattered expiratory wheezing, loose rales/crackles	Depressed air movement, inspiratory and expiratory wheezes or rales/crackles	Diminished or absent breath sounds, severe wheezing, or rales/crackles, or marked prolonged expiration
Use of Accessory Muscles	Mild to no use of accessory muscles, mild to no retractions, no nasal flaring on inspiration	Moderate intercostal retractions, mild to moderate use of accessory muscles, nasal flaring	Severe intercostal and substernal retractions, nasal flaring
Mental Status	Normal to mildly irritable	Irritable, agitated, restless.	Lethargic
Room Air SpO_2	>95%	90-95%	<90%
Color	Normal	Pale to normal	Cyanotic, dusky

(Add score from all rows to calculate total CRS score)

Table 2. *PALS Adjusted Vital Signs for Septic Shock*

Age	Heart Rate	Resp Rate	Systolic BP	Temp (°C)
0d - 1m	>205	>60	<60	<36 or >38
>1m - 3m	>205	>60	<70	<36 or >38
>3m - 1y	>190	>60	<70	<36 or >38.5
>1y - 2y	>190	>40	<70 + (age in yr x 2)	<36 or >38.5
>2y - 4y	>140	>40	<70 + (age in yr x 2)	<36 or >38.5
>4y - 6y	>140	>34	<70 + (age in yr x 2)	<36 or >38.5
>6y - 10y	>140	>30	<70 + (age in yr x 2)	<36 or >38.5
>10y - 13y	>100	>30	<90	<36 or >38.5
>13y	>100	>16	<90	<36 or >38.5

Table 3.
Signs and Symptoms of Shock

Exam Abnormalities			
	Cold Shock	**Warm Shock**	**Non-Specific**
Peripheral Pulses	Decreased or weak	Bounding	
Capillary Refill (central vs. peripheral)	≥3 sec	Flash (<1 sec)	
Skin	Mottled, cool	Flushed, ruddy, erythroderma (other than face)	Petechiae below the nipple, any purpura
Mental Status			Decreased, irritability, confusion, inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

Laboratory Tests:

- Obtain a complete blood count with reticulocyte count and note changes in baseline CBC or reticulocyte count or any laboratory abnormalities (such as increasing creatinine, liver function tests, coagulation abnormalities, etc.).
- Consider obtaining blood cultures if concerned for infectious pathology.
- Consider obtaining type and screen if concerned for need for transfusion.

Diagnostic Imaging Studies:

- Obtain a chest radiograph if patient has respiratory symptoms at presentation to the hospital or during admission. Fever in the absence of these symptoms does not necessitate evaluation with a chest radiograph.

Critical Points of Evidence*

Evidence Supports

- Collect complete blood count with differential, platelet count, reticulocyte count initially and daily for the patient with acute chest syndrome until the patient is improving. Results should be compared to the patient's baseline values. [4-7] – Strong recommendation, low quality evidence
- Collect secretory phospholipase A2 (sPLA2) levels for the suspicion of acute chest syndrome when the lab becomes available at Texas Children's Hospital. [7] – Strong recommendation, low quality evidence
- Obtain a chest radiograph if patient has cough, chest pain, hypoxemia, or lower respiratory symptoms at presentation to the hospital or during admission. Fever in the absence of these symptoms does not necessitate evaluation with a chest radiograph. [8-12] – Strong recommendation, very low quality evidence
- Encourage oral fluid intake and to administer total fluid intake (intravenous plus oral) at maintenance rate to encourage that the patient remains euvolemic. [13] – Strong recommendation, very low quality evidence
- Transfuse the patient with acute chest syndrome with PRBCs to a hemoglobin goal of 9-10 g/dL. [14,15] – Strong recommendation, very low quality evidence
- Use continuous pulse oximetry monitoring in patients with sickle cell disease who experiencing vaso-occlusive crisis who are being treated in the emergency center. [16-22] – Strong recommendation, very low quality evidence
- Encourage incentive spirometry in patients with sickle cell disease at risk for or with acute chest syndrome who are admitted to the hospital. [23-26] – Strong recommendation, low quality evidence
- Administer inhaled bronchodilators every 6 six to eight hours with acute illness if patient has a history of asthma or presents with wheezing. [23-26] – Strong recommendation, very low quality evidence
- Administer a one week course of prednisolone or three days of dexamethasone to patients who have clinical wheezing with or without a known history of asthma who are being treated in the inpatient setting. [27-31] – Strong recommendation, very low quality evidence
- Administer ketorolac in patients with mild to moderate pain. [32-34] – Strong recommendation, very low quality evidence
- Administer ketorolac as adjuvant therapy while initiating morphine via patient controlled analgesia for patients with severe pain (pain scores greater than seven). [32-34] – Strong recommendation, very low quality evidence

- Administer intranasal fentanyl or oral morphine for pain control in patients when there is a delay in IV placement. [35-38] – Strong recommendation, low quality evidence
- Try any non-pharmacologic intervention to help control pain. [39-44] – Strong recommendation, low quality evidence
- Use a high basal dose with a low on demand (intermittent opioid infusion) morphine via patient controlled analgesia in patients who present with pain crisis. Titrate depending on patient's pain control as determined by patient self-report of pain score. Once patient has achieved good control, wean until patients intravenous opioid dose can be transitioned to an oral dose. [45-49] – Strong recommendation, low quality evidence

Evidence Against

- Avoid corticosteroids unless indicated. [27-31] – Strong recommendation, very low quality evidence

Evidence Lacking/Inconclusive

- Progress to intrapulmonary percussive ventilation (IPV) or vest therapy if patient appears to be worsening. – Strong consensus recommendation
- Use of a risk score to predict health care utilization – Unable to make a recommendation
- Using functional pain scales as compared to traditional pain scales to assess pain in children – Unable to make a recommendation
- Administer antibiotics of symptoms suggest acute chest or if the patient has worsening respiratory distress. – Strong consensus recommendation

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

Consults/Referrals:

- Consult Pulmonary Service prior to discharge for CRS ≥5
- Consult Critical Care Medicine for CRS ≥4
- Consider Pain Service consult for: child hospitalized ≥3 days with no clinical improvement, avascular necrosis, unmanageable side effects from PCA, failure to control pain after titrating up and trying other agents, or complicated pain history
- Consider Child Life request to see for coping concerns and/or procedural preparations

Discharge Criteria:

- Improved pulmonary symptoms and documentation of adequate oxygenation on room air
- Afebrile ≥24 hours and negative cultures for ≥24-48 hours, if applicable
- Stable hemoglobin/hematocrit
- Taking adequate oral fluids and able to take PO medications, if applicable
- Adequate pain relief with oral analgesics, if applicable
- Slow wean from steroids (over 7-10 days), if applicable
- Home care agencies notified as needed

Caregiver understands:

- Discharge care, including steroid wean, if applicable
- When Hematology Clinic and Pulmonary SCD Clinic follow-ups scheduled
- How and when to use IS
- Medications and how to obtain them

Measures

Structure

- Availability of sPLA2 laboratory testing

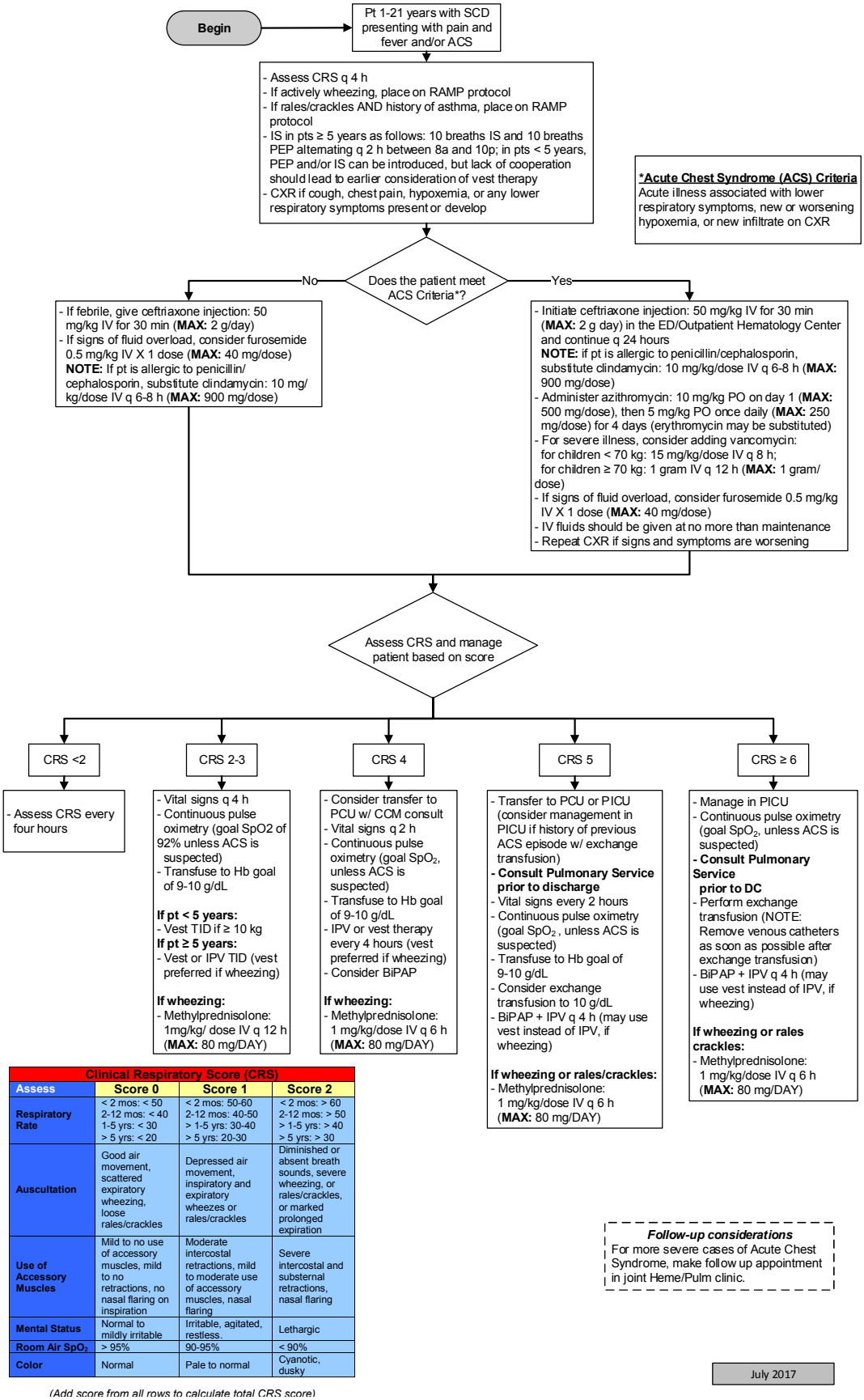
Process

- Order set utilization in the EC and inpatient units
- Documentation of CRS scores every 4 hours
- Incidence of pulmonary treatments
- Length of time on oxygen
- Frequency of ambulation
- Time to PCA initiation
- Percentage of patients with CRS ≥5 referred to pulmonary clinic
- Percentage of patients/caregivers who received IS and IS education
- CRS score of patients transferred to PCU/PICU
- Percentage of patients with documented RT consult upon arrival to unit

Outcome

- Number of patients who develop ACS
- Number of simple blood transfusions
- Number of exchange transfusions
- Number of patients transferred to the PCU or PICU
- ED and IP LOS
- Time on opioid
- Total PCA morphine dose
- Number of patients with ACS with identified pathogen
- Number of patients with unscheduled return visit to the ED/triage and/or admission for the same diagnosis within 14 days of discharge

Texas Children's Hospital Evidence-Based Outcomes Center
Sickle Cell Disease Respiratory Management Algorithm



Clinical Respiratory Score (CRS)			
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Auscultation	Good air movement, scattered expiratory wheezing, loose rales/crackles	Depressed air movement, inspiratory and expiratory wheezes or rales/crackles	Diminished or absent breath sounds, severe wheezing, or rales/crackles, or marked prolonged expiration
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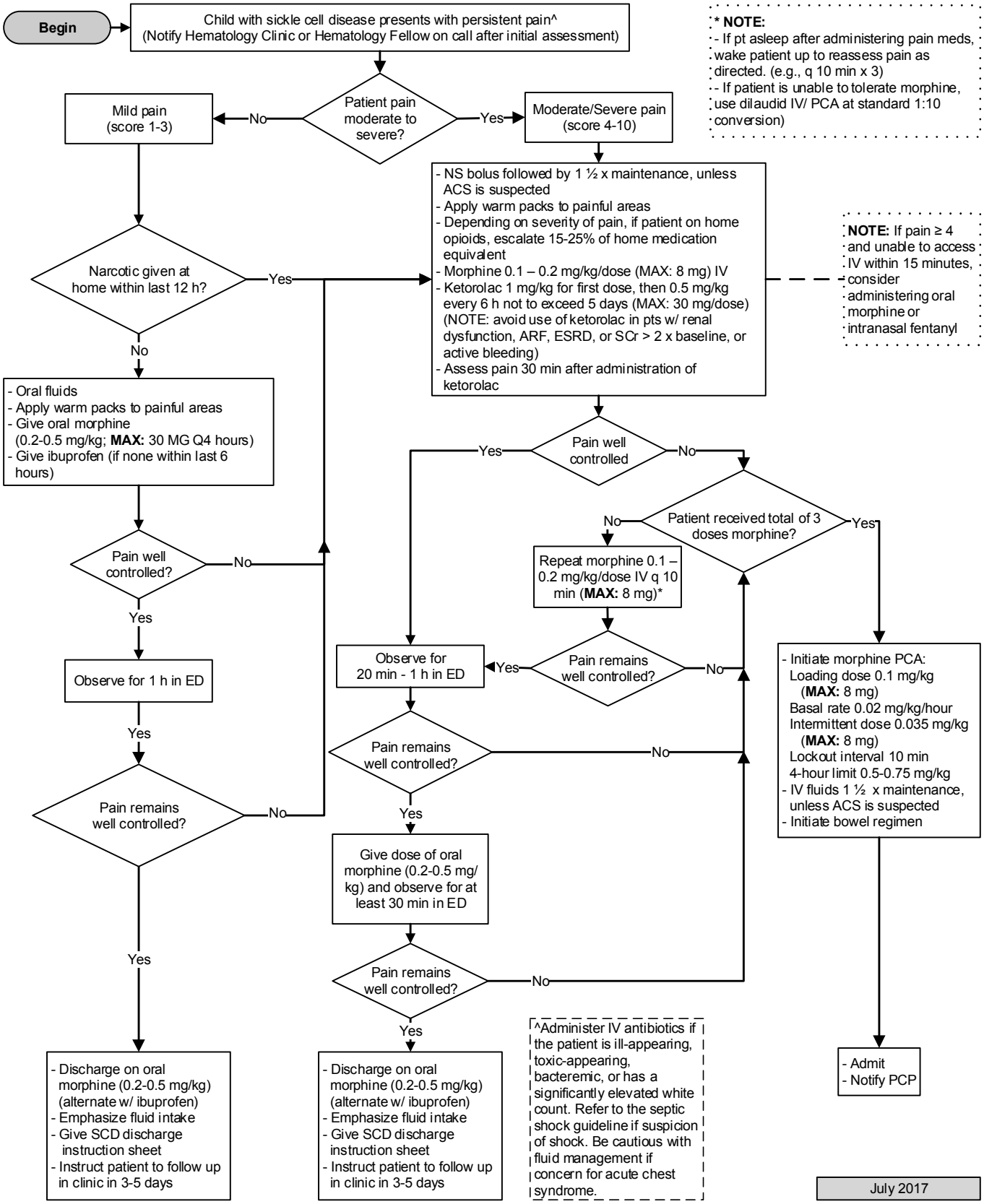
Mental Status	Normal to mildly irritable	Irritable, agitated, restless.	Lethargic
Room Air SpO_2	> 95%	90-95%	< 90%
Color	Normal	Pale to normal	Cyanotic, dusky

(Add score from all rows to calculate total CRS score)

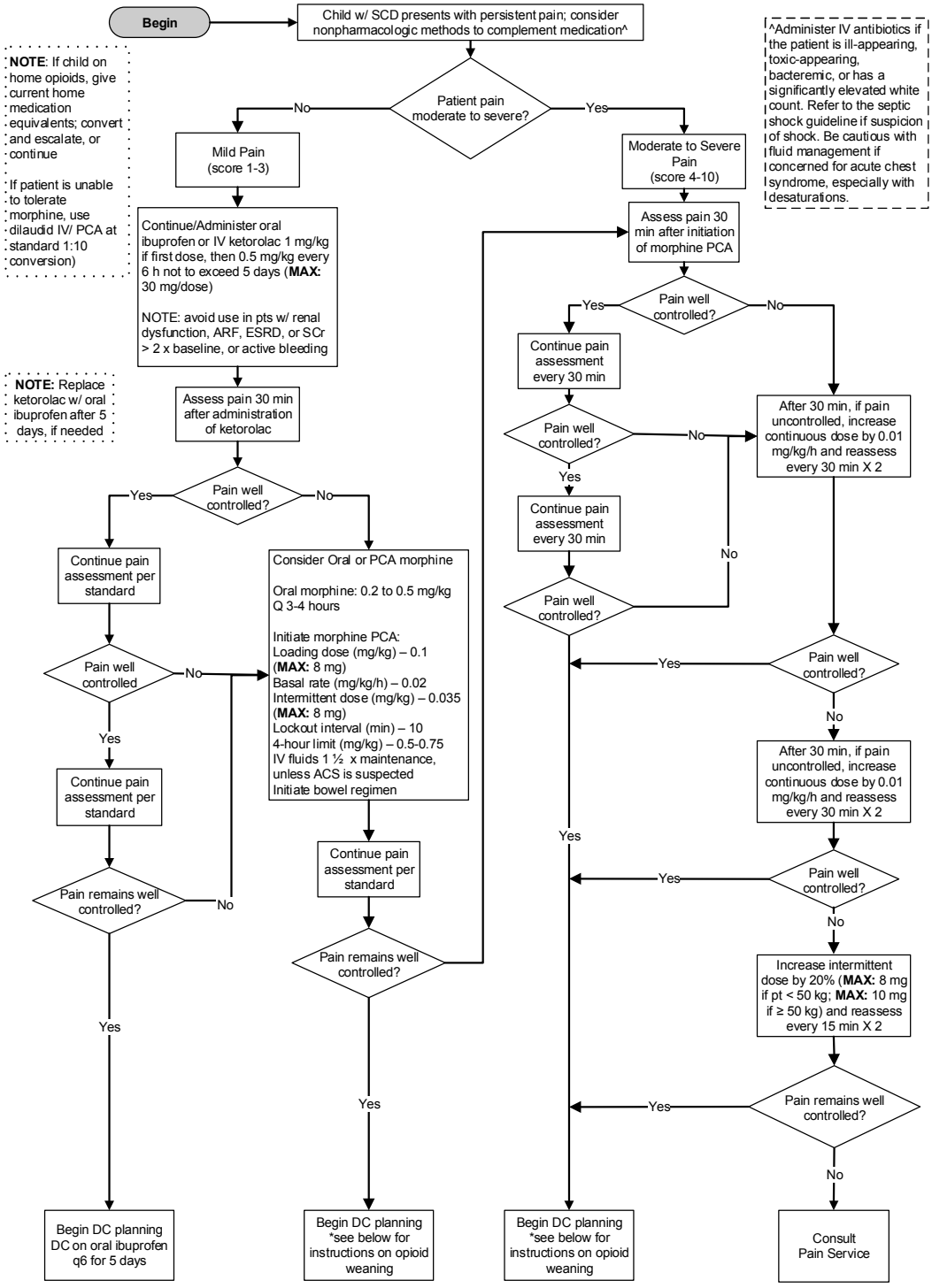
Follow-up considerations
For more severe cases of Acute Chest Syndrome, make follow up appointment in joint Heme/Pulm clinic.

July 2017

TCH Evidence-Based Outcomes Center
Emergency Department/Outpatient Hematology Center
Pain Management Algorithm for Patients With Sickle Cell Disease in Vaso-Occlusive Crisis



TCH Evidence-Based Outcomes Center
Sickle Cell Disease in Vaso-Occlusive Crisis Inpatient Pain Management Algorithm



NOTE: IVFs + PO intake should equal 1 ½ x maintenance, unless ACS is suspected. Wean IVFs according to patient oral intake.

NOTE: Rebalance opioid dose every 24 hours.

Instructions for opioid weaning:
- If pt's PCA demands are ½ of actual dose available, consider switching pt to oral meds (long-acting for basal, short-acting for bolus)
- If pt's condition improving and FLACC score has improved ≥ 2 measurements over 2 shifts, titrate down from continuous to long-acting
- Assess need for PCA every 24 h

Consider consulting Pain Service for:
- child hospitalized ≥ 3 days with no clinical improvement
- Avascular Necrosis (AVN)
- unmanageable side effects from PCA
- failure to control pain after titrating up and trying other agents
- complicated pain history

July 2017

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Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts

2. Review of Existing External Guidelines
   - Evidence-Based Management of Sickle Cell Disease Expert Panel Report (National Heart, Lung, and Blood Institute) 2014
   - Sickle Cell Disease: Managing acute painful episodes in hospital (National Institute for Clinical Excellence) 2012

3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane Library, CINAHL, Guidelines Clearinghouse, Google Scholar

4. Critically Analyze the Evidence
   - 3 meta-analyses, 15 randomized controlled trials, and 37 nonrandomized studies

5. Summarize the Evidence
   - Materials used in the development of the guideline, evidence summary, and order sets are maintained in a Vaso-occlusive Crisis in Sickle Cell Disease evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.
This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*.
The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

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, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of vaso-occlusive crisis in children with sickle cell disease. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards

(guidelines, summaries, or pathways) do not set out the standard of care, and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient family, to make the ultimate judgment regarding care

Version History

Date	Action	Comments
Jun 2011	Originally completed	
Jul 2017	Updated	