Clinical Pathways

Fever in a Patient with Sickle Cell Disease

Natalie Bezler, MD
Donna Boruchov, MD

Connecticut Children's

BEST CHILDREN'S HOSPITALS U.S.News RANKED IN 4 SPECIALTIES 2020-21

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

BEST CHILDREN'S HOSPITAL WOMEN'S CHOICE AWARD 2020

What is a Clinical Pathway?

An evidence-based guideline that decreases unnecessary variation and helps promote safe, effective, and consistent patient care.

Why is the pathway necessary?

- Fever is one of the most common chief complaints bringing patients with sickle cell disease to the Emergency Department at CT Children's
- A fever in these patients may be the first subtle sign of a serious bacterial infection and necessitates prompt evaluation (including a laboratory work-up and empiric antibiotic therapy) even if another source of fever is identified
- This pathway provides:
  - Specific criteria to risk-stratify patients and determine who warrants inpatient admission versus outpatient management with close follow-up
  - Strict discharge criteria
  - Ability to appropriately divert patients who present with sepsis and/or acute chest syndrome

Objectives of Pathway

- To improve triage and initial management of fever in patients with sickle cell disease in the emergency department and outpatient settings, through consistent application of current best practice
- To decrease the time from initial presentation to first evaluation by a provider and administration of empiric antibiotic therapy
- To decrease the number of patients admitted to the hospital by appropriately discharging patients who can be managed outpatient with close follow-up

Background

- Patients with sickle cell disease are often functionally asplenic by age three years of age
  - Are at increased risk of severe bacterial infection, particularly encapsulated bacteria
  - The most notably pathogens include *S. pneumoniae*, as well as *H. influenzae*, *N. meningitidis*, and salmonellae[2]
- Although vaccinations and antibiotic prophylaxis has made bacteremia increasingly rare (rates of 0.8% or lower[1,8]), the risk of overwhelming bacterial infection necessitates that infection be ruled out

This is the Fever in a Patient with Sickle Cell Disease Clinical Pathway.

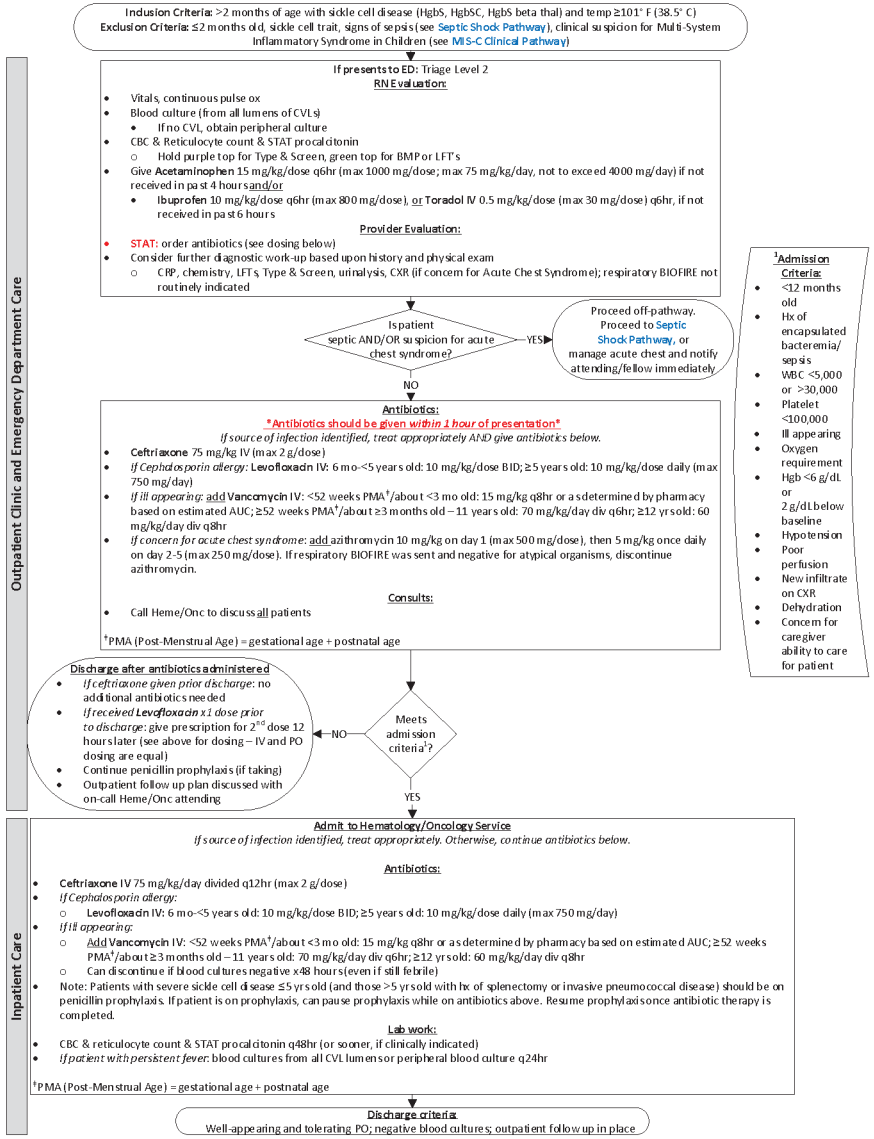
This pathway spans outpatient clinic, emergency department, and inpatient care.

We will be reviewing each component in the following slides.

CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

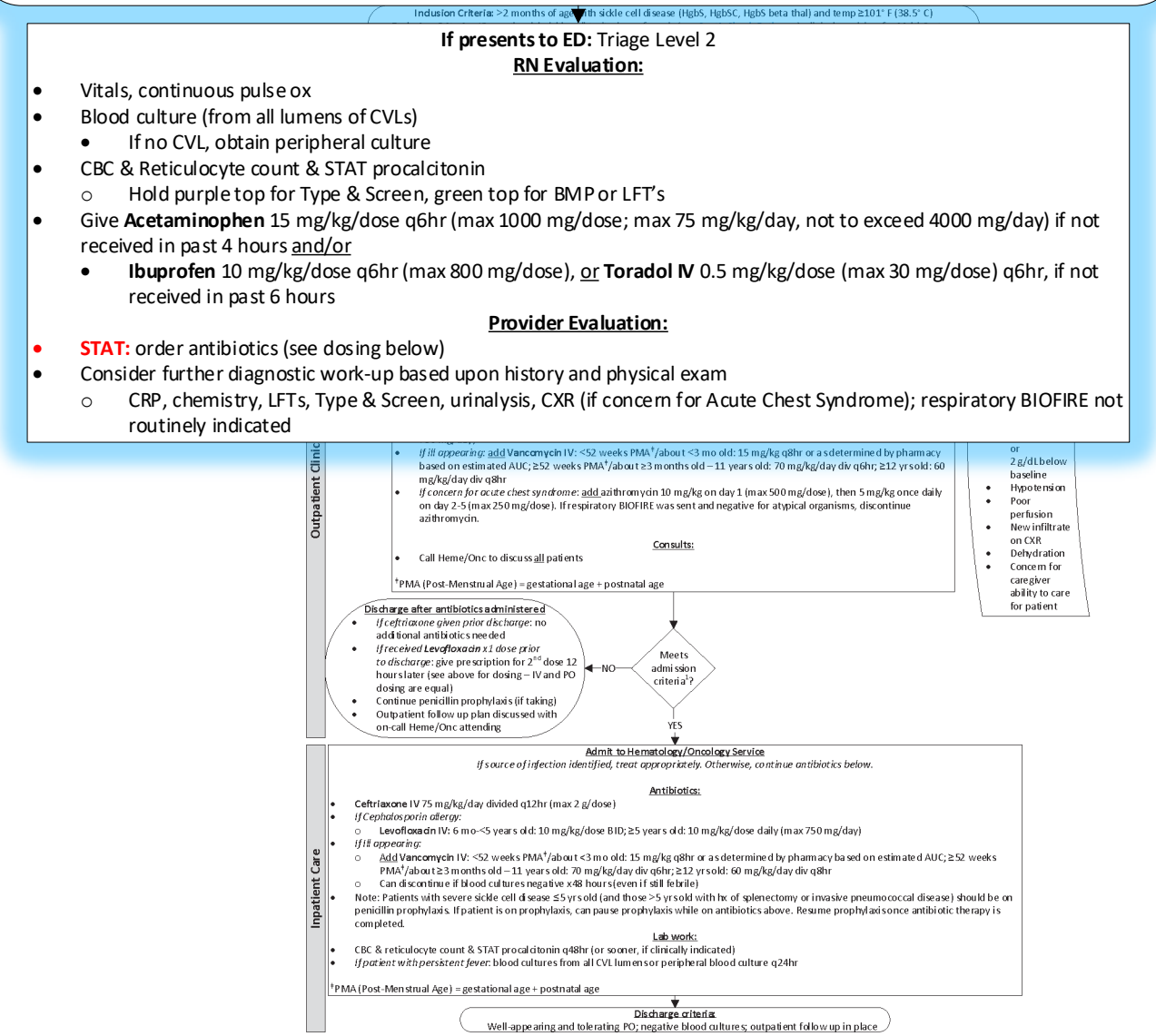
LAST UPDATED: 06.06.23

- Inclusion and Exclusion criteria are clearly defined.
- Those with Sickle Cell Disease are included while those with Sickle Cell Trait are excluded.
- Patients with septic shock and MIS-C should be treated off of this pathway.

CLINICAL PATHWAY:

THIS PATHWAY

Inclusion Criteria: >2 months of age with sickle cell disease (HgbS, HgbSC, HgbS beta thal) and temp ≥101° F (38.5° C)
Exclusion Criteria: ≤2 months old, sickle cell trait, signs of sepsis (see **Septic Shock Pathway**), clinical suspicion for Multi-System Inflammatory Syndrome in Children (see **MIS-C Clinical Pathway**)



CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

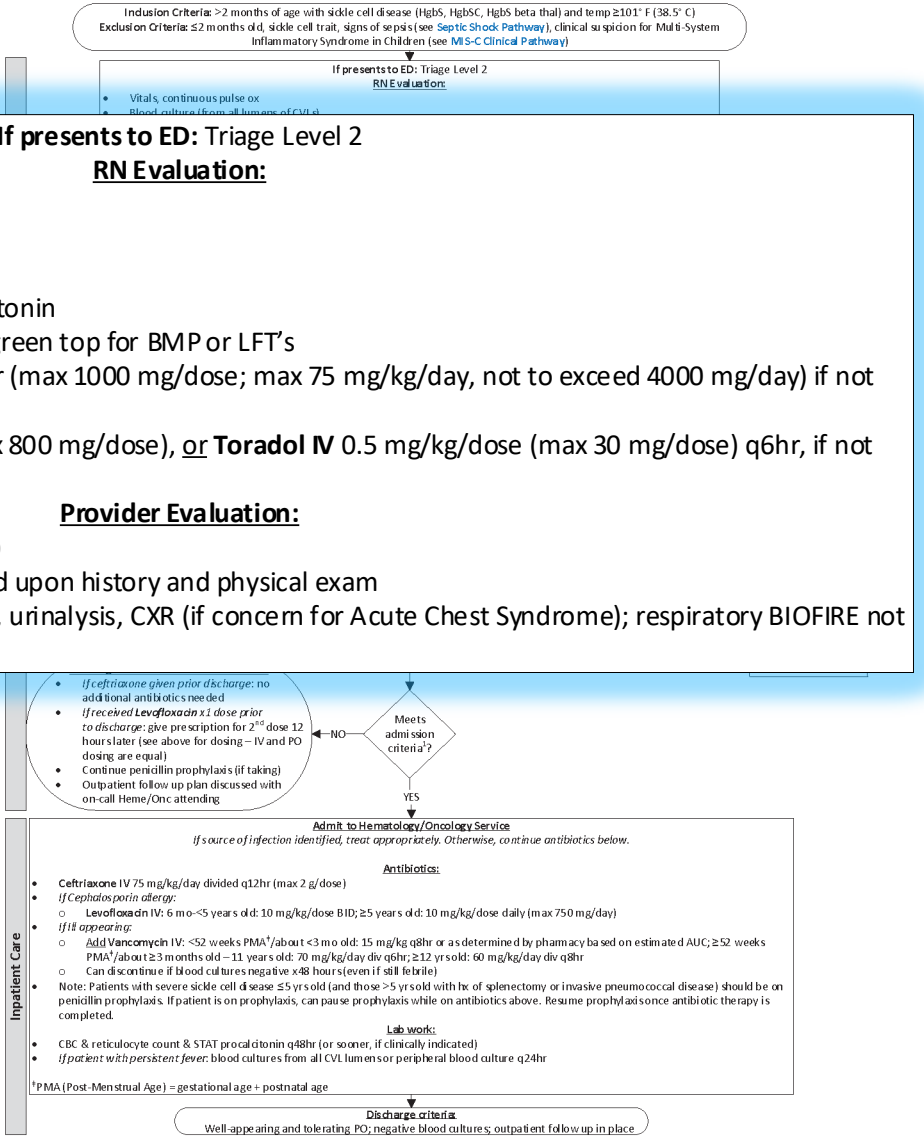
LAST UPDATED: 06.06.23

- If the patient has a CVL, blood cultures should be obtained from all lumens
  - Otherwise, peripheral blood cultures should be drawn
- Procalcitonin has been shown to be unaffected by vaso-occlusive disease in patients with SCD
  - This can help differentiate between fever due to infection vs inflammation[9]
- Of note, respiratory BIOFIRE is not routinely indicated

CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

LAST UPDATED: 06.06.23

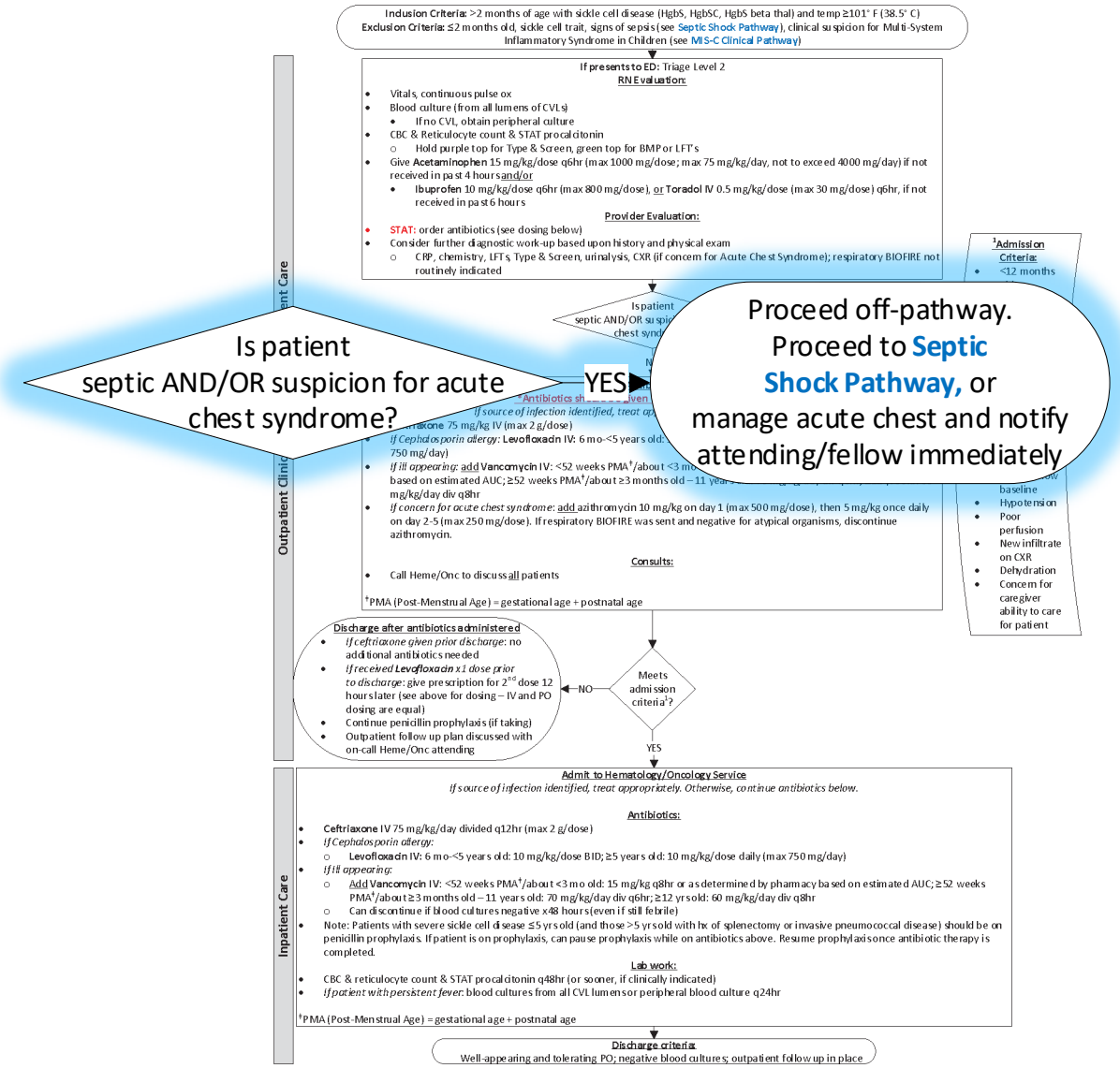
If there is concern for sepsis AND/OR suspicion for acute chest syndrome:

- The patient should be managed off-pathway.
- Proceed to Septic Shock Clinical Pathway or manage acute chest
- Notify the attending/fellow immediately
- Timely identification and management are important!

CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

LAST UPDATED: 06.06.23

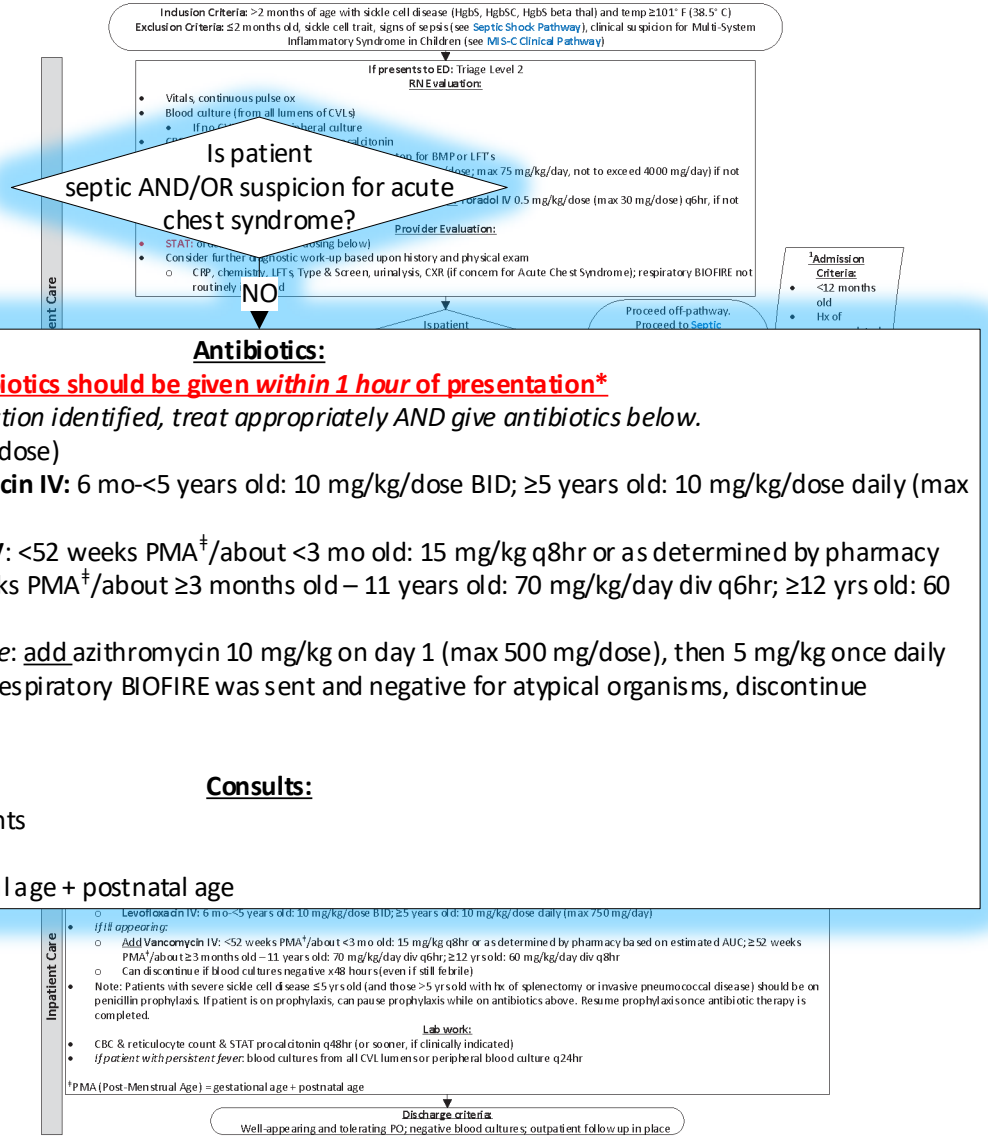
If there is no suspicion of septic shock or acute chest syndrome, the patients can proceed with this pathway.

- **Antibiotics should be given within 1 hour of presentation**
- All patients should receive empiric antibiotic therapy, **even if the source of the fever has been identified**, with additional appropriate treatment based on source
- Heme/Onc should be consulted to discuss **all** patients

CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



Antibiotics:

Antibiotics should be given *within 1 hour* of presentation

If source of infection identified, treat appropriately AND give antibiotics below.

- **Ceftriaxone** 75 mg/kg IV (max 2 g/dose)
- *If Cephalosporin allergy:* **Levofloxacin IV:** 6 mo-<5 years old: 10 mg/kg/dose BID; ≥5 years old: 10 mg/kg/dose daily (max 750 mg/day)
- *If ill appearing:* add **Vancomycin IV**: <52 weeks PMA‡/about <3 mo old: 15 mg/kg q8hr or as determined by pharmacy based on estimated AUC; ≥52 weeks PMA‡/about ≥3 months old – 11 years old: 70 mg/kg/day div q6hr; ≥12 yrs old: 60 mg/kg/day div q8hr
- *If concern for acute chest syndrome*: add azithromycin 10 mg/kg on day 1 (max 500 mg/dose), then 5 mg/kg once daily on day 2-5 (max 250 mg/dose). If respiratory BIOFIRE was sent and negative for atypical organisms, discontinue azithromycin.

Consults:

- Call Heme/Onc to discuss all patients

‡PMA (Post-Menstrual Age) = gestational age + postnatal age

CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

LAST UPDATED: 06.06.23

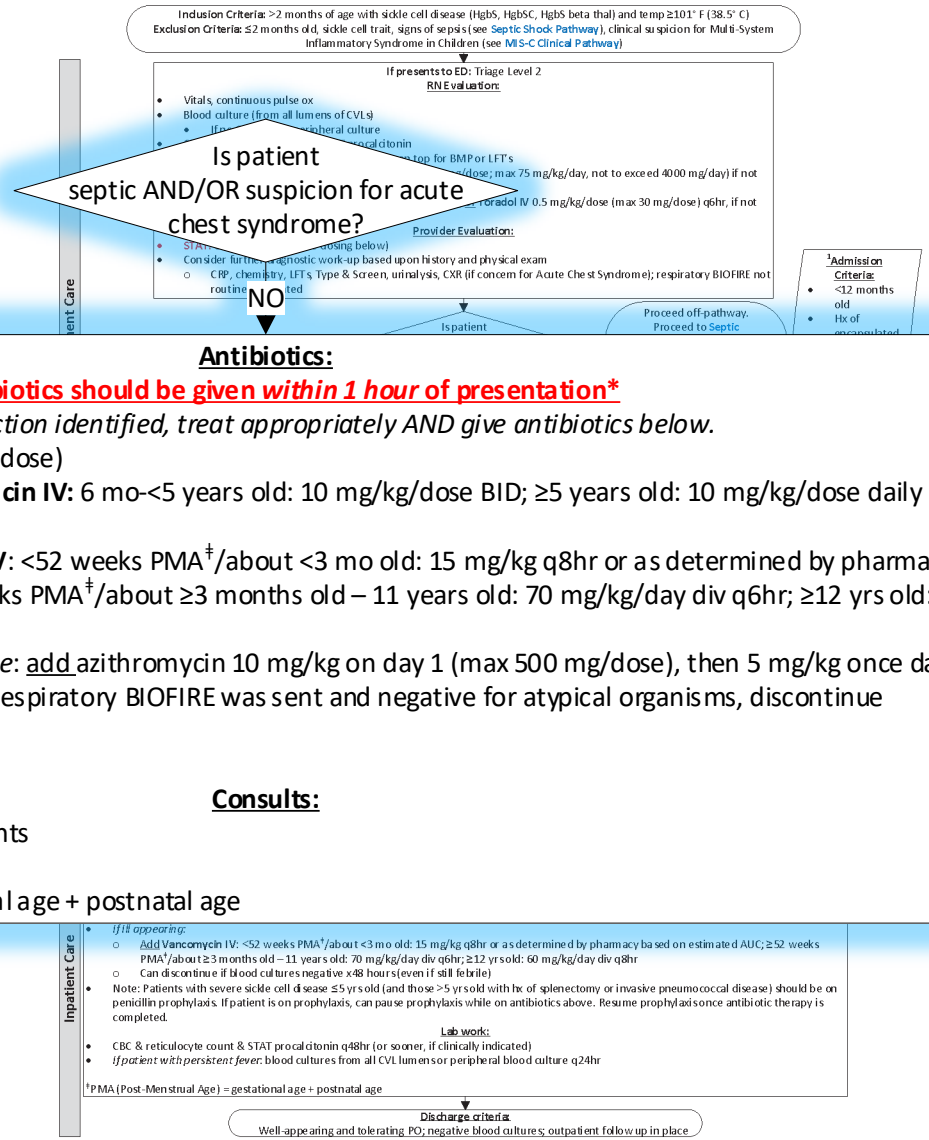
Connecticut Children's

- Ceftriaxone provides good coverage for the most common invasive organisms, including strep pneumo and H. influenza
- If there is a cephalosporin allergy, levofloxacin can be used.
  - *Note: dosing has been updated to be in line with Lexicomp and current susceptibility patterns*
- If ill appearing, add vancomycin
- If concerns for acute chest syndrome, azithromycin should be added.

CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



Antibiotics:

Antibiotics should be given *within 1 hour* of presentation

If source of infection identified, treat appropriately AND give antibiotics below.

- **Ceftriaxone** 75 mg/kg IV (max 2 g/dose)
- *If Cephalosporin allergy:* **Levofloxacin IV:** 6 mo-<5 years old: 10 mg/kg/dose BID; ≥5 years old: 10 mg/kg/dose daily (max 750 mg/day)
- *If ill appearing:* add **Vancomycin IV**: <52 weeks PMA‡/about <3 mo old: 15 mg/kg q8hr or as determined by pharmacy based on estimated AUC; ≥52 weeks PMA‡/about ≥3 months old – 11 years old: 70 mg/kg/day div q6hr; ≥12 yrs old: 60 mg/kg/day div q8hr
- *If concern for acute chest syndrome*: add azithromycin 10 mg/kg on day 1 (max 500 mg/dose), then 5 mg/kg once daily on day 2-5 (max 250 mg/dose). If respiratory BIOFIRE was sent and negative for atypical organisms, discontinue azithromycin.

Consults:

- Call Heme/Onc to discuss all patients

‡PMA (Post-Menstrual Age) = gestational age + postnatal age

CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

LAST UPDATED: 06.06.23

- Patients who do **not** meet admission criteria can be discharged home after receiving empiric antibiotics
  - Those who received ceftriaxone may be discharged home without additional antibiotics
  - Those who received levofloxacin must be given a Rx for a 2nd dose to cover a total of 24 hours
- If the patient is on penicillin prophylaxis, they should continue taking it
- Outpatient follow up plans should be discussed with the on-call Heme/Onc attending

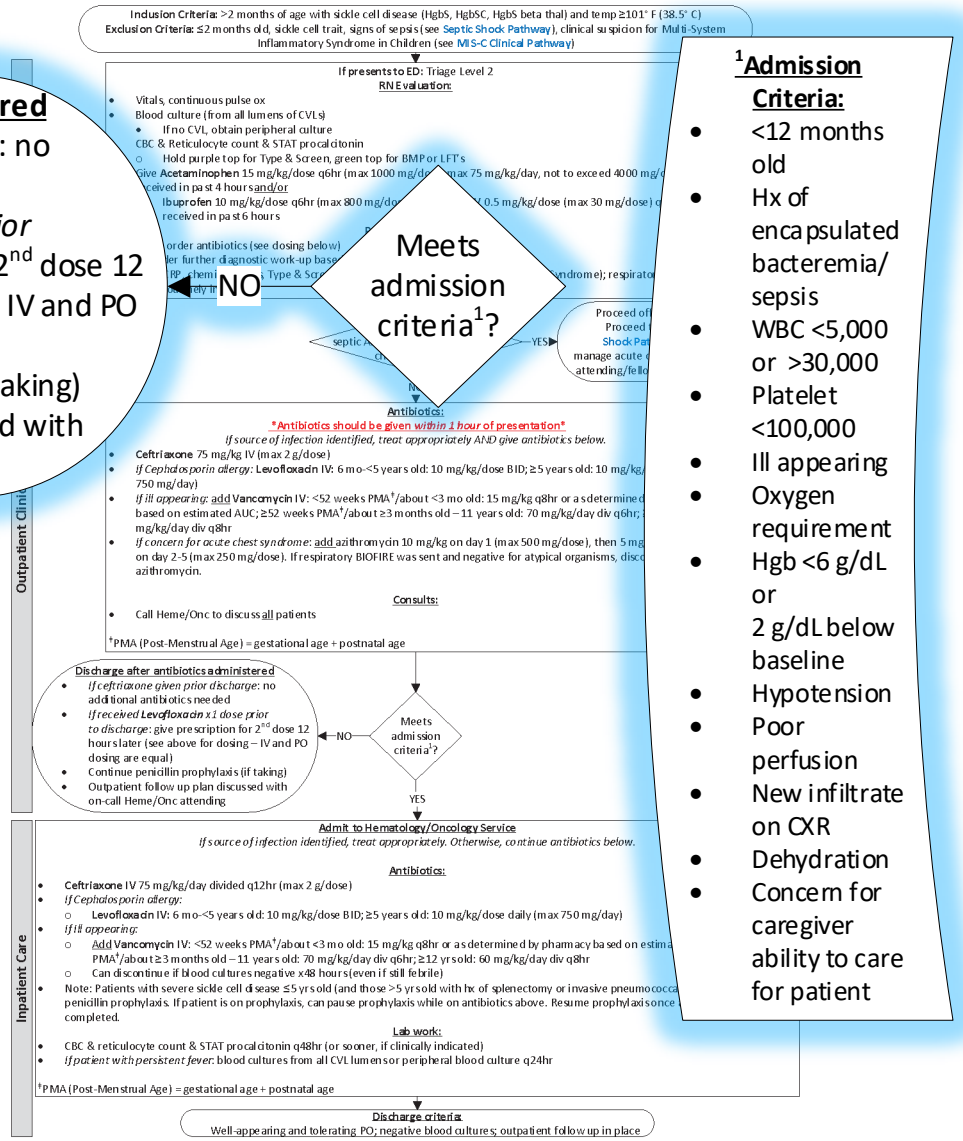
CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

Discharge after antibiotics administered

- *If ceftriaxone given prior discharge*: no additional antibiotics needed
- *If received **Levofloxacin** x1 dose prior to discharge*: give prescription for 2nd dose 12 hours later (see above for dosing – IV and PO dosing are equal)
- Continue penicillin prophylaxis (if taking)
- Outpatient follow up plan discussed with on-call Heme/Onc attending



[1]Admission Criteria:

- <12 months old
- Hx of encapsulated bacteremia/ sepsis
- WBC <5,000 or >30,000
- Platelet <100,000
- Ill appearing
- Oxygen requirement
- Hgb <6 g/dL or 2 g/dL below baseline
- Hypotension
- Poor perfusion
- New infiltrate on CXR
- Dehydration
- Concern for caregiver ability to care for patient

CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

LAST UPDATED: 06.06.23

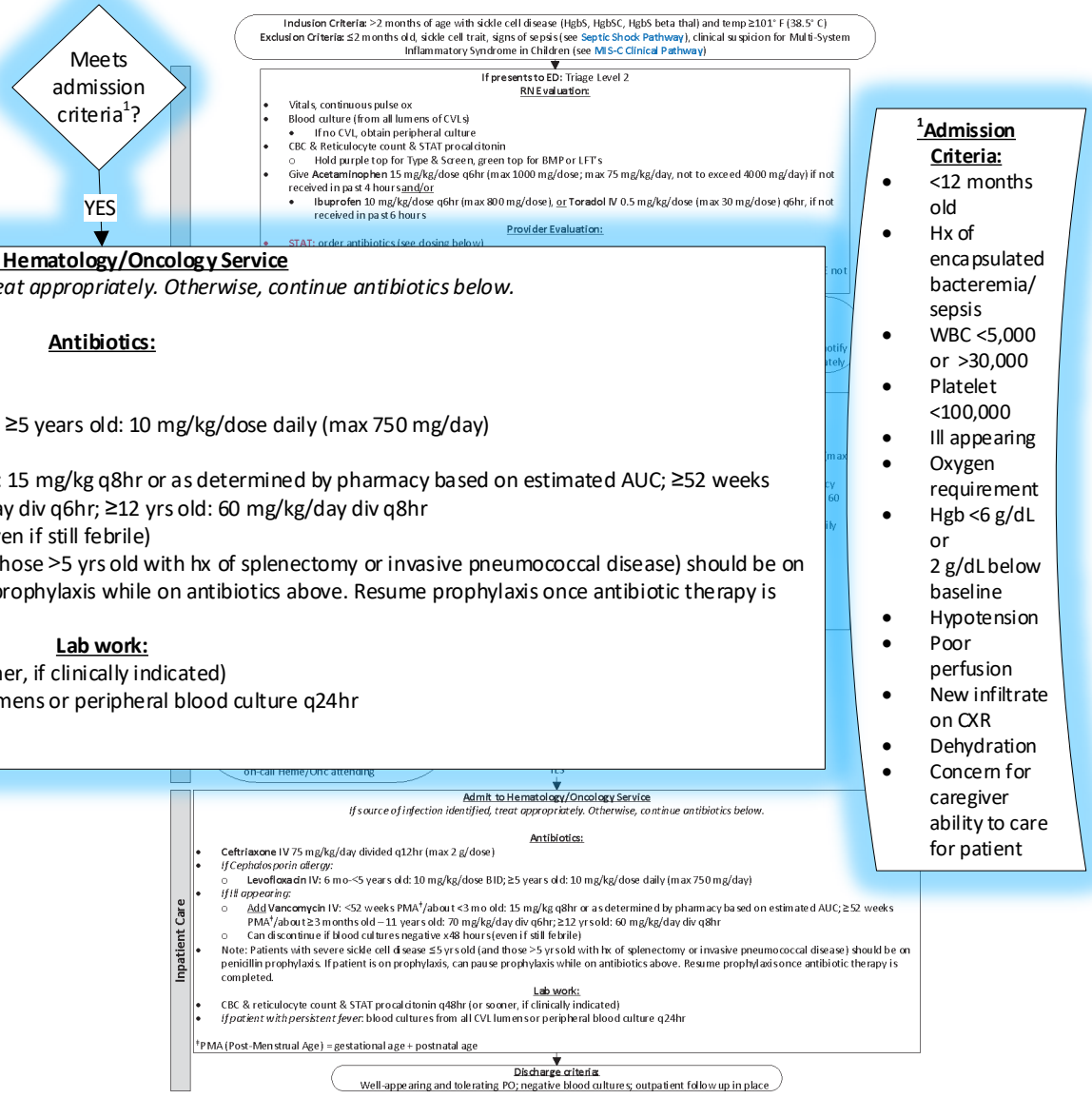
Connecticut Children's

- Patients who meet ANY ONE of the admission criteria must be admitted to the Heme/Onc service
- If the source of fever has been identified, treat based on infection source
- If the source has not been identified, continue with empiric antibiotics
- Note that patients who require penicillin prophylaxis can pause their prophylaxis while on inpatient antibiotics. It should be resumed once antibiotic therapy is completed.

CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



Admit to Hematology/Oncology Service

If source of infection identified, treat appropriately. Otherwise, continue antibiotics below.

Antibiotics:

- **Ceftriaxone IV** 75 mg/kg/day divided q12hr (max 2 g/dose)
- *If Cephalosporin allergy:*
  - **Levofloxacin IV:** 6 mo-<5 years old: 10 mg/kg/dose BID; ≥5 years old: 10 mg/kg/dose daily (max 750 mg/day)
- *If Ill appearing:*
  - Add **Vancomycin IV**: <52 weeks PMA‡/about <3 mo old: 15 mg/kg q8hr or as determined by pharmacy based on estimated AUC; ≥52 weeks PMA‡/about ≥3 months old – 11 years old: 70 mg/kg/day div q6hr; ≥12 yrs old: 60 mg/kg/day div q8hr
  - Can discontinue if blood cultures negative x48 hours (even if still febrile)
- Note: Patients with severe sickle cell disease ≤5 yrs old (and those >5 yrs old with hx of splenectomy or invasive pneumococcal disease) should be on penicillin prophylaxis. If patient is on prophylaxis, can pause prophylaxis while on antibiotics above. Resume prophylaxis once antibiotic therapy is completed.

Lab work:

- CBC & reticulocyte count & STAT procalcitonin q48hr (or sooner, if clinically indicated)
- *If patient with persistent fever*: blood cultures from all CVL lumens or peripheral blood culture q24hr

‡PMA (Post-Menstrual Age) = gestational age + postnatal age

[1]Admission Criteria:

- <12 months old
- Hx of encapsulated bacteremia/ sepsis
- WBC <5,000 or >30,000
- Platelet <100,000
- Ill appearing
- Oxygen requirement
- Hgb <6 g/dL or 2 g/dL below baseline
- Hypotension
- Poor perfusion
- New infiltrate on CXR
- Dehydration
- Concern for caregiver ability to care for patient

CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

LAST UPDATED: 06.06.23

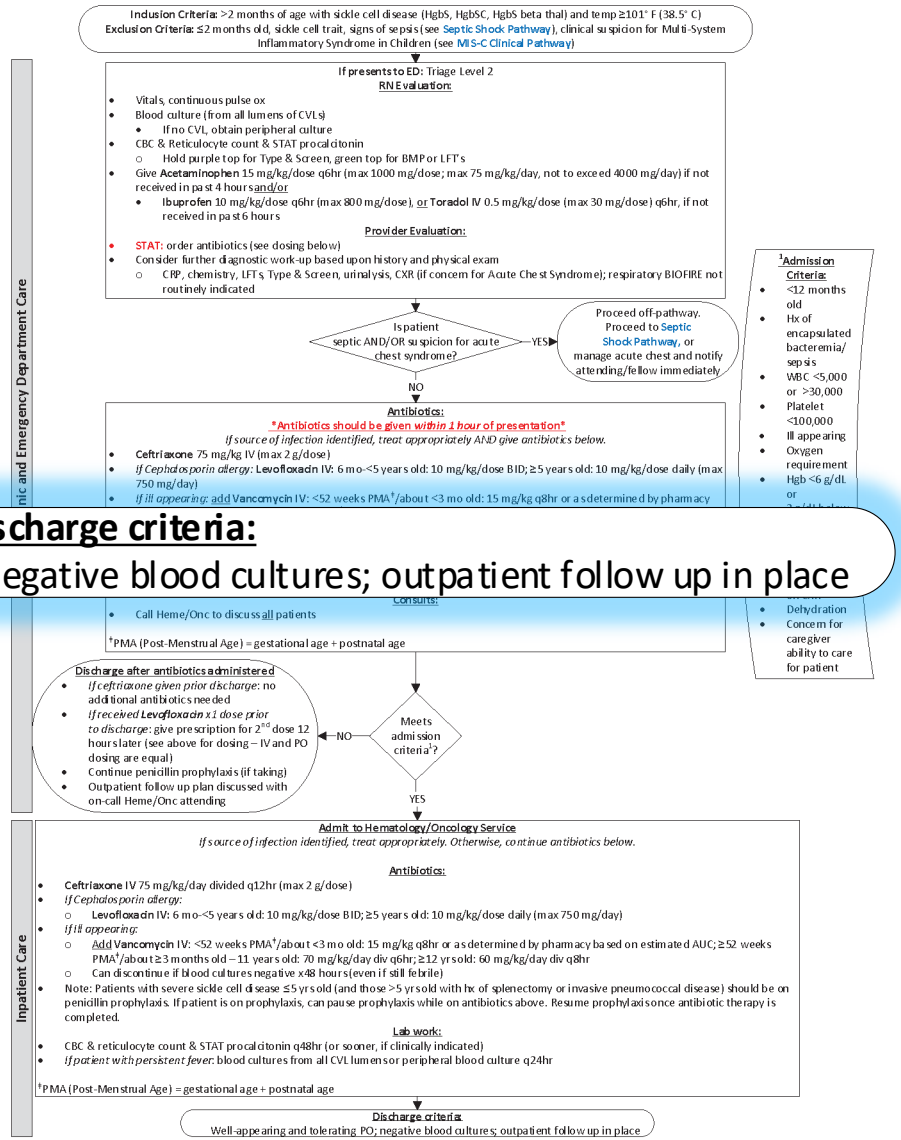
Connecticut Children's

Once patient meets discharge criteria, they may be sent home with close follow up in place.

CLINICAL PATHWAY:

Fever in a Patient with Sickle Cell Disease

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



Discharge criteria:

Well-appearing and tolerating PO; negative blood cultures; outpatient follow up in place

CONTACTS: NATALIE BEZLER, MD | DONNA BORUCHOV, MD

LAST UPDATED: 06.06.23

Connecticut Children's

Review of Key Points

- Administration of antibiotics within 1 hour of presentation is very important
- If a source of fever is identified, give empiric antibiotics *in addition* to treating the source
- Patients who meet any of the admission criteria must be admitted to the Hematology-Oncology service

Quality Metrics

- Percentage of eligible patients treated per clinical pathway
- Length of time from arrival to ED/clinic to administration of antibiotics OR length of time from first fever documented, while inpatient, to administration of antibiotics
- Percentage of patients receiving appropriate antibiotic at correct dose
- Length of stay in ED/clinic (minutes) and hospital (days)
- Percentage of patients appropriately admitted to the hospital

Pathway Contacts

- Natalie Bezler, MD
  - Division of Hematology/Oncology
- Donna Boruchov, MD
  - Division of Hematology/Oncology

References

1. Baskin M, Goh X, Heeney M, Harper M. Bacteremia Risk and Outpatient Management of Febrile Patients With Sickle Cell Disease. *Pediatrics*. 2013;131(6):1035-41.
2. Booth C, Inusa B, Obaro S. Infection in sickle cell disease: A review. *International Journal of Infectious Diseases*. 2010;14:e2-e12.
3. Ellison A, Smith Whitley K, Kittick M, Schast A, Norris C, Hartung H, et al. A Standardized Clinical Pathway to Decrease Hospital Admissions Among Febrile Children With Sickle Cell Disease. *Journal of Pediatric Hematology/Oncology*. 2018;40(2):111-5.
4. Ender KL, Krajewski JA, Babineau J, Tresgallo M, Schechter W, Saroyan JM, Kharbanda A. Use of a clinical pathway to improve the acute management of vaso-occlusive crisis pain in pediatric sickle cell disease. *Pediatric Blood & Cancer*. 2014;61(4):693-6.
5. Loberger J, Polley K. Improving the Time to Antibiotics in Febrile Children with Sickle Cell Disease in the Emergency Department. *Pediatrics*. 2018;141(1).
6. Morrissey BJ, Bycroft TP, Almossawi O, Wilkey OB, Daniels JG. Incidence and Predictors of Bacterial infection in Febrile Children with Sickle Cell Disease. *Hemoglobin.* 2015;39(5):316-9.
7. National Heart, Lung, and Blood Institute. Evidence-Based Management of Sickle Cell Disease. Expert Panel Report. Bethesda, MD: National Institutes of Health; 2014.
8. Shihabuddin BS, Scarfi CA. Fever in Children With Sickle Cell Disease: Are All Fevers Equal? *Journal of Emergency Medicine*. 2014 October 2014;47(4):395-400.
9. Unal S, Arslankoylu A, Kuyucu N, Aslan G, Erdogan S. Procalcitonin is More Useful Than C-reactive Protein in Differentiation of Fever in Patients With Sickle Cell Disease. *Journal of Pediatric Hematology/Oncology*. 2012;34(2):85-89.

Thank You!

About Connecticut Children's Pathways Program

Clinical pathways guide the management of patients to optimize consistent use of evidence-based practice. Clinical pathways have been shown to improve guideline adherence and quality outcomes, while decreasing length of stay and cost. Here at Connecticut Children's, our Clinical Pathways Program aims to deliver evidence-based, high value care to the greatest number of children in a diversity of patient settings. These pathways serve as a guide for providers and do not replace clinical judgment.