Inclusion Criteria:
• Sickle Cell Disease
• Fever ≥ 38.6°C

Exclusion Criteria:
• Sickle Cell trait
• Hb S/E (see patient chart for algorithm)
• Child ≤ 56 days old. See Neonatal Fever pathway

Sickle Cell Care

Fever

Appendix

Version Changes Approval & Citation Evidence Ratings Bibliography

For questions concerning this pathway, contact: SickleCellPathway@seattlechildrens.org
If you are a patient with questions contact your medical provider, Medical Disclaimer
Sickle Cell Pathway v2.2: Fever

Inclusion Criteria:
- Sickle Cell Disease
- Fever ≥ 38.6°C

Exclusion Criteria:
- Sickle Cell trait
- Hb S/E (see patient chart for algorithm)
- Child ≤ 56 days old. See Neonatal Fever pathway

High Risk Criteria for Infection
- <6mo
- Splenectomized
- History of bacteremia with an encapsulated organism
- Barriers to timely follow-up
- <5 years and not on prophylactic antibiotics (h/o of no PCN prophylaxis)
- O2 need (Saturations <94%)
- Multiple ED evals for the same febrile illness
- Temp. ≥ 40°C

Begin fever work-up
- Physical exam, vital signs, cardiopulmonary assessment, hydration status, spleen size and neurologic exam
- Order chest x-ray, CBC, reticulocyte count, blood culture, urinalysis, and urine culture.
- If concern for osteomyelitis or septic joint, consult Orthopedics
- If meningitis is suspected, perform lumbar puncture
- If central line, see Central Line Infection Pathway

Antibiotics
- Parenteral (IM or IV) antibiotics within 60 minutes
- Repeat vital signs and assessment at 30 and 60 minutes after antibiotics

Is patient ill-appearing or do they meet high risk criteria for infection?

No
Consider additional factors that may influence the decision to admit
Decision to discharge. Communicate with Heme/Onc on call.
Discharge to home with 3 days of oral antibiotic. Follow up the next day with PCP or OBCC in person or by telemedicine. ED follow-up if other options not available.

Yes
Decision to admit

Admit for continued parenteral antibiotics
Observe inpatient until culture (-) for 24 hours
If afebrile for 24 hours, discontinue parenteral antibiotics, consider discharge. Resume PCN if applicable and follow up if fever returns.

If culture (+), ill appearing, or temp. ≥ 40°C
If culture (+), treat as per organism
If afebrile for 24 hours, discontinue parenteral antibiotics and consider discharge. Resume PCN if applicable and follow up if fever returns.

At re-evaluation 18-24 hours after the initial ceftriaxone dose

If culture (-), well appearing, and temp. 38.6-39.9°C
If culture (-), well appearing, and temp. <38.6°C for 24 hours

Follow-up every 3-4 days. Continue oral antibiotics until afebrile for 24 hours.
Complete 3 day course of oral antibiotics.
Resume PCN prophylaxis if appropriate.

Additional Discharge Criteria
- Adequate oral intake, and able to take oral medications (if needed)
- Pain and other medical complications resolved to an extent to allow discharge.
- Hematologic labs not concerning
- Follow-up scheduled if indicated.

Discharge Instructions
- Review signs and symptoms of infection and when to return for fever.

For questions concerning this pathway, contact: SickleCellPathway@seattlechildrens.org

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Sickle Cell Definition

Sickle Cell definition
Sickle Cell disease includes Hb S/S, HbS/C, Hb S/β0-thalassemia, Hb S/β+-thalassemia, Hb S/D, Hb S/O-Arab and all other compound heterozygotes with HbS that lead to a severe sickling phenotype. This includes patients with high HbF, but excludes those with documented HbS/HPFH (Hereditary Persistence of Fetal Hemoglobin-typically listed in sickle cell problem list). This also excludes forms with HbS but that do not lead to increased rates of bacteremia and frequent vaso-occlusion episodes including Hb S/E and sickle cell trait (Hb A/S).
ill appearing includes, but is not limited to:

a. Pain with inspiration
b. Tachypnea, shallow breathing, grunting or splinting
b. Lower respiratory tract symptoms
c. Inability to self hydrate
d. Pain requiring IV opiates
e. Appears listless, lethargic, or irritable
f. Decreased perfusion

Return to Fever
Discharge Oral Antibiotics

If discharged from the ED or inpatient with fever send home with a three day supply of oral antibiotic:

Amoxicillin / Clavulanic acid
  If allergic send home with Ciprofloxacin and Clindamycin

Timing of starting oral antibiotics
  - If last dose of parenteral antibiotic at night, then start the following evening.
  - If last dose of parenteral antibiotic during the day, then start the following morning
  * If given parenteral Cipro and Clinda instead of CTX, Abx should be given sooner.
Additional factors weighing into decision to admit

Additional factors weighing into decision to admit (per expert opinion):
1. Major Factors
   a. WBC >30k.  (lowers threshold to admit, especially if on hydroxyurea).
   b. Additional medical complications (e.g. pain, splenic sequestration, asthma, etc.)
   c. Significantly behind in immunizations, especially for encapsulated origins

2. Lesser Factors
   a. <3yr
   b. Hgb drop <2g/dl from baseline or significant drop in reticulocyte count
   c. PLT <100k
   d. Fall in O2 saturations below baseline but still >93%
   e. Antipyretic or NSAID within 6 hours of when temperature measured

3. Having  Hb S/C or S/β+ thalassemia is a minor factor in raising the threshold to admit

Return to Fever
Ceftriaxone Induced Hemolytic Anemia

Ceftriaxone can lead to a drug induced hemolytic anemia which can result in a sudden, dramatic, often lethal anemia:

- It is unpredictable, and not well characterized.
- People with sickle cell appear to be an increased risk.
- Presentation is often precipitous and within 30 minutes.
  - Pallor, diaphoresis, emessis, hypotension, shock are common.
  - The Hgb can fall 3-10g/dl within minutes (~10-30 hct points)
  - A high index of suspicion is critical
- Post-CTX monitoring is critical (60 minutes)
- Treatment: If suspicious- initiate immediate massive transfusion protocol, IVIg and high dose steroids
- Diagnosis: Send sample to blood bank stating you are looking for a Drug induced hemolytic anemia to ceftriaxone. Blood is often visually altered upon drawing.

Return to Fever
Summary of Version Changes

- **Version 1.1 (4/15/2013):** Go live
- **Version 1.2 (3/20/2015):** Algorithm wording correction to align with powerplan.
- **Version 1.3 (2/8/2019):** Contact e-mail updated
- **Version 2.0 (10/3/2020):** Periodic review go live; standardized workup and management of patients with sickle cell and fever, defining fever as $\geq 38.6^\circ$ C.
- **Version 2.1 (4/15/2021):** Algorithm update to clearly define that children admitted with sickle cell and fever should be observed until culture is negative for 24 hours.
- **Version 2.2 (6/22/2021):** Added clarification with the words “(if needed)” to the first bullet in the Additional Discharge Criteria box.
Approval & Citation

Approved by the CSW Sickle Cell Pathway team for October 3, 2020 go-live

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Retrieval Website: https://www.seattlechildrens.org/pdf/sickle-cell-algorithm.pdf

Evidence Ratings

This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94, Hultcrantz M et al. J Clin Epidemiol. 2017;87:4-13.):

Quality ratings are **downgraded** if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are **upgraded** if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

**Certainty of Evidence**
- 🌟🌟🌟🌟 High: The authors have a lot of confidence that the true effect is similar to the estimated effect
- 🌟🌟🌟 Moderate: The authors believe that the true effect is probably close to the estimated effect
- 🌟🌟 Low: The true effect might be markedly different from the estimated effect
- 🌟 Very low: The true effect is probably markedly different from the estimated effect

Guideline: Recommendation is from a published guideline that used methodology deemed acceptable by the team
Expert Opinion: Based on available evidence that does not meet GRADE criteria (for example, case-control studies)
**Literature Search Methods**
For this update, search strategies were revised in line with current Library practices. Literature searches were conducted in two phases: a synthesis-level search performed in April 2019 on sickle cell disease or acute chest syndrome; and an expanded search performed in September 2019 on diagnosis of bacterial infections or febrile presentations in patients with sickle cell disease. The synthesis search was executed in Ovid Medline, Embase, Cochrane Database of Systematic Reviews (CDSR), and Turning Research into Practice database (TRIP); results limited to English, 2009 to current. The expanded search was executed in Ovid Medline and Embase; results were limited English, 1946 to current.

Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers independently screened abstracts and included guidelines and systematic reviews that addressed optimal diagnosis, treatment, and prognosis of patients who meet pathway inclusion/exclusion criteria. One reviewer screened full text and extracted data and a second reviewer quality checked the results. Differences were resolved by consensus.

**Literature Search Results**
The searches of the four databases (see Electronic searches) retrieved 1533 records. Our searches of other resources identified 1 additional records that appeared to meet the inclusion criteria.

Once duplicates had been removed, we had a total of 1148 records. We excluded 1089 records based on titles and abstracts. We obtained the full text of the remaining 59 records and excluded 43. Sixteen articles were included.

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535
Included Studies


Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

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