Table 4: Evidence Supporting Anticipatory Guidance of the Prevention and/or Management of Fever and Severe Infection in Children with Sickle Cell Disease

Type of evidence	Key findings	Level of evidence (USPSTF ranking*)	Citation(s)
Clinical guidelines	The goal [of newborn screening] is to identify all newborns with SCD and start them on prophylactic penicillin as early as possible. The recommended regimen is: Newborn to 3 years: Penicillin VK, 125 mg orally twice daily 3 to 5 years: Penicillin VK, 250 mg orally twice daily.	III	National Heart Lung and Blood Institute. The Management of Sickle Cell Disease. National Institutes of Health. Bethesda, MD, 2002.
Consensus guidelines	In 1987, multiple braches of the NIH convened a consensus panel to discuss newborn screening for SCD. The panel notes that, because babies with sickle cell disease may develop sepsis as young as 4 months of age, early provision of comprehensive care coupled with prophylactic penicillin therapy beginning prior to age 4 months is now recommended.	III	Consensus conference. Newborn screening for sickle cell disease and other hemoglobinopathies. *JAMA* 1987; 258(9):1205-1209.
Comprehensive literature review	In a comprehensive review of the literature on the management of children with sickle cell disease by Kavanagh et al., the authors searched for articles on this topic published between 1995 and 2010. They found eight articles related to penicillin prophylaxis for the prevention of life threatening infection in children with SCD. Of these articles, three provided level I evidence, one provided level II evidence and four provided level III evidence rated using the USPSTF scale.	III	Kavanagh PL, Sprinz PG, Vinci SR, Bauchner H, Wang CJ. Management of children with sickle cell disease: a comprehensive review of the literature. *Pediatrics* 2011;128(6):e1552-1574.
Meta-analysis	A meta-analysis of three randomized trials found that initiation of penicillin prophylaxis for children with SCD under age 5 years significantly reduced the incidence of pneumococcal infection (OR: 0.37 [95% CI 0.16 – 0.86]).	III	Hirst C, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database of Systematic Reviews* 2010; 1-21.
Randomized controlled trial	In a randomized, double-blind, placebo controlled trial, Gaston et al. studied whether daily administration of oral penicillin reduced the incidence of life-threatening infection in children with SCD. In the trial, 215 children under the age of 3 were randomly assigned to receive either 125 mg penicillin or placebo twice daily. The study was ended early because of an 84% reduction in incidence of infection	I	Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med* 1986; 314(25):1593-1599.

Type of evidence	Key findings	Level of evidence (USPSTF ranking*)	Citation(s)
	among the intervention group.		
Clinical guidelines	One of the key principles in the management of febrile children with SCD is that parents and clinicians should be taught that a temperature over 38.5 degrees C is an emergency. All children with SCD who have fever greater than 38.5 degrees Celsius or 101 degrees Fahrenheit and other signs of infection should be evaluated promptly. The younger the child, the higher the index of suspicion. In a child with no obvious sources of infection, a minimum evaluation should include blood culture, complete blood count, reticulocyte count, and chest x-rays for children less than 3 years of age. Immediately after the blood is taken, the child should be given broad-spectrum antibiotics, preferably intravenously. Broad spectrum antibiotics should be given even if these tests cannot be performed. Ideally, children with SCD are followed at a practice or center that allows for comprehensive management of their disease. These facilities should have 24-hour access to medical consultants, hematology and microbiology laboratories, and a blood bank, among other services.	III	National Heart Lung and Blood Institute. The Management of Sickle Cell Disease. National Institutes of Health. Bethesda, MD, 2002.
Clinical guidelines	The goal of ensuring timely medical treatment for acute illness also is facilitated by providing anticipatory guidance to patients and families about early recognition, appropriate medical evaluation, and treatment of common acute complications. Discussing the need for urgent medical evaluation for fever should be part of family education and acute illness planning from birth through childhood and adolescence. Because patients with SCD develop splenic dysfunction at as early as 3 months of age, they are at high risk for septicemia and meningitis with pneumococci and other encapsulated bacteria. Thus, all patients with temperature greater than 38.5 degrees C require rapid triage and physical assessment, urgent CBC and reticulocyte counts, blood culture (plus cerebrospinal fluid analysis and other cultures as indicated), and prompt administration of a broad-spectrum parenteral antibiotic, such as ceftriaxone sodium, cefuroxime, or cefotaxime	III	American Academy of Pediatrics Section on Hematology/Oncology and Committee on Genetics. Health supervision for children with sickle cell disease. *Pediatrics*. Mar 2002;109(3):526-535.

Type of evidence	Key findings	Level of evidence (USPSTF ranking*)	Citation(s)
	sodium.		
Clinical guidelines	Because acute illness can prove rapidly life-threatening, it is imperative that every child with SCD have a plan for around-the-clock access to a medical facility where knowledge and perspective about SCD is available, evaluation and treatment promptly delivered, and providers have access to baseline information about the patient. Children with SCD with a temperature greater than 38.5 degrees C should be promptly administered IV ceftriaxone (50-100 mg/kg, 2.0 maximum dose…Relatively high doses (75-100 mg/kg) are sometimes recommended in regions with high prevalence of antibiotic resistant S. pneumoniae.	III	Lane PA, Buchanan GR, Hutter JJ, et al. Sickle cell disease in children and adolescents: diagnosis, guidelines for comprehensive care, and care paths and protocols for management of acute and chronic complications. 2001; Annual Meeting of the Sickle Cell Disease Care Consortium, Sedona, AZ. Nov. 10-12, 2001. http://txch.org/wp-content/uploads/sickle-cell-disease-guidelines-complications.pdf; accessed March 20, 2014.
Clinical guidelines	Children with SCD with a fever greater than or equal to 38.5 degrees C should be given parenteral broad spectrum antibiotic treatment within 60 minutes of triage.	III	Wang CJ et al. Quality-of- care indicators for children with sickle cell disease. *Pediatrics* 2011; 128:484-493.

Note: USPSTF criteria for assessing evidence at the individual study level are as follows: I) Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or meta-analysis of homogeneous RCTs. II) Well-designed cohort or case-control analytic study. III) Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.