EVIDENCE REPORT

Evidence-Based Management of Sickle Cell Disease

Expert Panel Report, 2014

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

Fever

Background

People with SCA have an increased risk of severe bacterial infection, resulting primarily from reduced or absent splenic function.[162] By 2 or 3 months of age, as their fetal hemoglobin declines, infants with SCA begin to develop splenic impairment. The result is an extremely high risk of septicemia and meningitis, primarily due to *Streptococcus pneumoniae*. Although the incidence of invasive pneumococcal infection has declined as a result of prophylactic penicillin and pneumococcal vaccination, febrile illnesses in people with SCD are still considered an emergency due to the possibility of penicillin-resistant organisms and incomplete vaccination status. The risk of such infections continues throughout childhood and to a lesser extent in adults. Serious infections can also affect persons with other forms of SCD (e.g., HbSC and HbSβ^+-thalassemia).
As a presenting symptom, fever heralds many acute and sometimes life-threatening conditions, such as ACS and osteomyelitis. In many cases, the cause of fever is unclear, but because individuals with SCA have a highly increased risk of overwhelming bacterial infection, it is critical that fever alone is taken seriously in these individuals and considered a potential emergency situation. Fever associated with pain should not be considered a VOC until infection is ruled out.

People with SCD who develop fever may have ACS due to diverse organisms (including *Mycoplasma*) and are also at risk of gram-negative enteric infections involving the urinary tract, hepatobiliary system, or bones. Acute osteomyelitis, another complication associated with fever, may be unifocal or multifocal and may be caused by *Staphylococcus aureus*, salmonella, or other enteric pathogens. Persons with SCD have normal T cell and B cell function, so the risk of acute infection is generally limited to those micro-organisms mentioned above. Opportunistic infections are infrequent.

Summary of the Evidence

An adequate systematic review of the literature with fair sensitivity and specificity for all studies indexed by SCD terms and the symptom of fever was not feasible. A large and nonspecific return of studies with significant heterogeneity, high miss rate, and low-quality evidence (lack of comparative studies) was anticipated. No systematic review was conducted, and the panel used a consensus process to develop a proposed strategy for triaging and promptly managing fever.

Recommendations

1. In people with SCD and a temperature ≥101.3°F (38.5°C), immediately evaluate with history and physical examination, complete blood count (CBC) with differential, reticulocyte count, blood culture, and urine culture when urinary tract infection is suspected.
   (Consensus–Panel Expertise)
2. In children with SCD and a temperature ≥101.3 °F (38.5 °C), promptly administer ongoing empiric parenteral antibiotics that provide coverage against *Streptococcus pneumoniae* and gram-negative enteric organisms. Subsequent outpatient management using an oral antibiotic is feasible in people who do not appear ill.
   (Consensus–Panel Expertise)
3. Hospitalize people with SCD and a temperature ≥103.1 °F (39.5 °C) and who appear ill for close observation and intravenous antibiotic therapy.
   (Consensus–Panel Expertise)
4. In people with SCD whose febrile illness is accompanied by shortness of breath, tachypnea, cough, and/or rales, manage according to the preceding recommendations and obtain an immediate chest x ray to investigate for ACS.
   (Consensus–Panel Expertise)

Recommendations
5. In febrile people with SCD who have localized or multifocal bone tenderness, especially when accompanied by erythema and swelling, include bacterial osteomyelitis in the differential diagnosis and manage accordingly. ***(Consensus–Panel Expertise)***

Acute Renal Failure

Background

Acute renal failure (ARF) is defined here as a rapid reduction in renal function manifested by a rise in serum creatinine and reduction in glomerular filtration rate (GFR), with or without a decline in urine output. ARF may be due to pre-renal (e.g., dehydration) or post-renal (e.g., obstruction) insults, or result from intrinsic renal disease (e.g., glomerular injury). ARF may occur during an acute VOC, most often in association with ACS or acute multisystem organ failure (MSOF).[163]

Renal papillary necrosis due to medullary infarction from obstruction of the blood supply in the vasa recta affects up to 15–30 percent of individuals with SCD.[164] Signs and symptoms include flank pain and hematuria. When present, fever suggests possible superinfection.

ARF may also occur when individuals with chronic sickle cell nephropathy or other chronic kidney diseases are exposed to nephrotoxic medications (e.g., NSAIDs or intravenous contrast dye) or become dehydrated. People with SCD often display a relative inability to maximally concentrate the urine, resulting in increased vulnerability to pre-renal azotemia.

Due to increased renal tubular secretion of creatinine, serum creatinine values in SCD do not rise until significant renal impairment occurs (GFR of 30 mL/min or less).[39] Since the serum creatinine levels are generally low or low-normal in individuals with SCD, the values in ARF may still be within normal limits even if they have doubled from baseline. It is important to consider non-SCD-related causes of ARF before simply attributing ARF to SCD.[165]

When associated with acute MSOF attributed to diffuse vaso-occlusion, ARF may respond to exchange red blood cell transfusion.[163,166] However, the benefit of transfusion for other causes of ARF in SCD has not been reported. Acute and chronic renal replacement therapy, including hemodialysis, is well-tolerated by people with SCD and should be used when indicated.[163,167]

Key Question

KQ11. In people with SCD and ARF, what are the most effective strategies to reduce mortality and the risk of developing end-stage renal disease (ESRD)?

Summary of the Evidence

The systematic review did not identify comparative studies to demonstrate the superiority of a particular diagnostic or therapeutic approach to ARF in people with SCD. The literature in this area was mostly descriptive of people who developed renal complications (e.g., hyposthenuria, hematuria, impaired urinary potassium excretion and acidification, tubular and glomerular dysfunction, infection, medullary carcinoma, acute necrosis and renal failure).