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Prevention and Management of Infection in Children with Sickle Cell Anaemia

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Contents

Abstract

Sickle cell anaemia (SCA) predisposes a child to infections for various reasons, including increased bone marrow turnover, poor perfusion and functional asplenia leading to decreased opsonisation of polysaccharide encapsulated organisms. Bacteria and viruses that most frequently cause serious infections in children with sickle cell disease are *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Salmonella* spp., *Escherichia coli, Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, parvovirus B19 and hepatitis A, B and C viruses.

Penicillin prophylaxis has decreased the incidence of infection-related morbidity and mortality significantly in children with SCA. Children <3 years of age are administered oral penicillin 125mg twice daily, and the dose is increased to 250mg twice daily for the >3 to 5 year age group. Adherence to the penicillin prophylactic regimen is recommended for children with SCA who are >5 years of age. For children with SCA who have recurrent invasive pneumococcal infections, an effort is made to keep the child on penicillin prophylaxis indefinitely.

The administration of various childhood vaccines has also made an appreciable impact on the overall morbidity and mortality associated with infection in

children with SCA. The administration of the heptavalent conjugate pneumococcal vaccine (PCV7) has provided control of invasive pneumococcal infections, and the prophylactic use of the *H. influenzae* type b conjugate vaccine has reduced the incidence of septicaemia and meningitis caused by this organism. Other vaccines used prophylactically in children with SCA include hepatitis A and B, and vaccines against influenza and varicella viruses.

The immediate administration of intravenous antibacterials, after appropriate blood and urine cultures, is of great importance in the treatment of the febrile child with SCA. Ceftriaxone and cefotaxime have been recommended for the treatment of septic episodes in SCA associated with *S. pneumoniae*, *Haemophilus* and *Salmonella* spp. Infection with *Yersinia enterocolitica* may be treated with cefotaxime or an aminoglycoside. The prevalence of *Helicobacter pylori* infection in SCA is unknown. Effective therapies include metronidazole, tetracycline or amoxicillin. Parvovirus infections require supportive care and specific antiviral therapy is not indicated.

The judicious use of antimicrobials is encouraged in view of the worldwide emergence of multidrug-resistant strains. The long term sequelae associated with infections in children with SCA can be decreased with the implementation of immunisation programmes and effective and prompt treatment with appropriate antibacterials.

Children with sickle cell anaemia (SCA) have an increased susceptibility to certain infections by virtue of their underlying disease for various reasons:

- functional asplenia compromises immunity to polysaccharide-encapsulated organisms
- poor perfusion and bone infarction predisposes to osteomyelitis
- chronic haemolytic anaemia with increased red cell precursor turnover in the bone marrow makes them vulnerable to parvovirus infection and aplastic crises
- frequent blood transfusions expose them to viral and other blood-borne infections
- transfusion-related iron-overload renders them susceptible to specific organisms such as *Yersinia enterocolitica.*

1. Common Causes of Infections

The increased incidence of infections from polysaccharide-encapsulated organisms in children with SCA has been well documented.[1-3] However, the risks of succumbing to infections from other organisms should also be considered.

The most common cause of septicaemia, pneumonia and meningitis is *Streptococcus pneumoniae* despite prophylactic use of penicillin and pneumococcal vaccines. The incidence of pneumococcal septic arthritis is rare. Osteomyelitis and septic arthritis are more commonly associated with *Salmonella sp.*, *Escherichia coli*, other Gram-negative organisms and, occasionally, *Staphylococcus aureus*. Urinary tract infections with *E. coli* should be suspected in cases of fever and no other identifiable source of infection as it can be asymptomatic in some cases. *Haemophilus influenza type b* used to be a common pathogen in SCA sepsis and meningitis, but as stated earlier, incidence of infection has been well-controlled with effective vaccines.[4] Other organisms associated with frequent infections in SCA include *Mycoplasma* and *Chlamydia pneumoniae* for symptoms of pneumonia and/or acute chest syndrome, and *parvovirus B19* for aplastic anaemia and hepatitis A, B and C.

Of note, the SCA population is also more susceptible to *Yersenia enterocolitica* if chronically transfused and *Helicobacter pylori* have been diagnosed in children presenting with abdominal pain.

The advent of an effective *Haemophilus influenzae* conjugate vaccine has reduced overall

morbidity and mortality in children with SCA.[4] The incidence of *S. pneumoniae* bacteraemia and meningitis has also decreased substantially in the past 15 years.[5,6] The case fatality rate caused by pneumococcal infection was 35% prior to 1972, had fallen to18% by 1981, and with the use of the 23-valent pneumococcal vaccine is currently at about 12.5%.[5,6] However, resistant strains and break-through infections are still commonly reported. Serotypes 6, 14, 18, 19 and 23 accounted for 74% of the cases of bacteraemia, and serotype 6 accounted for 33% of the cases of meningitis with an increasing incidence of serotype 9 infections.[7,8]

We need to reinforce our efforts at prevention and treatment in order to effectively decrease the morbidity and mortality associated with such invasive infections.

2. Prevention

2.1 Penicillin Prophylaxis

The widespread use of penicillin prophylaxis, effective parental education and participation, as well as early diagnosis and treatment through neonatal screening have significantly decreased infection-related morbidity and mortality in children with SCA. Children <3 years old should be administered oral penicillin125mg twice daily with the dose increased to 250mg twice daily for the >3 to 5 year age group. Penicillin prophylaxis should be initiated as early as possible, preferably by 4 months of age.[9] For patients with a penicillin allergy, erythromycin can be used as an alternative. We should not assume a sense of complacency with the knowledge that a child has been placed on penicillin prophylaxis. A number of children who succumbed to overwhelming infections were already receiving penicillin prophylaxis and immunised with the age-appropriate vaccines.[10,11] In these children, previous antibacterial use has been associated with a greater risk for systemic pneumococcal infections caused by penicillin-resistant isolates.[12]

2.2 Stopping Penicillin Prophylaxis

A discussion with the family regarding the benefits and difficulties with continuing twice daily penicillin prophylaxis should occur prior to the child's fifth birthday. Keeping to the prophylactic regimen past 5 years of age is often difficult for families. Buchanan et al.,[13] Berkovitch et al.,[14] and Teach et al.,[15] have demonstrated a compliance rate of 50 to 70%. As a compromise to stopping prophylaxis at 5 years of age, prompt institution of oral antibacterials (penicillin or amoxicillin) at home and immediate medical attention in the event of a fever provides adequate coverage, pending a complete medical evaluation, and administration of intravenous antibacterials if warranted. Based on the findings of a multicentre study of children with SCA,[16] which showed no difference in the rate of invasive pneumococcal infection among the children receiving penicillin prophylaxis and those receiving placebo after 5 years of age, the current recommendation for stopping penicillin prophylaxis stands at 5 years of age, after the second dose of the 23-valent vaccine. However, in the child with SCA who experiences recurrent invasive pneumococcal infections, an effort should be made to keep the child on penicillin prophylaxis indefinitely.[17]

2.3 Immunisations

The importance of childhood vaccines that should be given to the child with SCA must be stressed, particularly for those children receiving frequent blood transfusions, i.e. the hepatitis A and B series, meningococcal and influenza vaccines, and varicella vaccine. However, breakthrough varicella infections are not uncommon. The immunisation schedule for the latter vaccines is similar to that given to other children as part of their normal care. Meningococcal vaccine should be given at ≥2 years of age.

The availability of the 7-valent conjugated pneumococcal vaccine (PCV7) has provided hope for the control of breakthrough invasive pneumococcal infections. A single efficacy trial has been

completed with 37 868 children randomised to receive either PCV7 or a meningococcal vaccine conjugated to diphtheria cross-reacting molecule 197 (MenCRM). Three cases of vaccine serotype-specific invasive disease were reported in children randomised to receive PCV7 versus 49 cases in the MenCRM group, with a 93.9% efficacy ($p < 0.0001$).[18] Recent reports on children with SCA showed that immunoglobulin G (IgG) pneumococcal antibody levels were higher in children receiving the combined schedule of PCV7 followed by 23-valent pneumococcal vaccine, and no increase in adverse effects was observed.[19,20] Therefore, a combination of the newer 7-valent vaccine given in infancy and early childhood, augmented by the 23-valent vaccine, should be given. PCV7 will not protect against nonvaccine type pneumococci and the eventual impact of the vaccine against pneumococcal infections is yet unknown. There is a possibility of capsular serotype switching over time as well as increases in nonvaccine type disease because of replacement with existing strains of nonvaccine type pneumococci in the nasopharynx. Continued vigilance and surveillance for serotype and strain switching should be maintained to monitor this effect.

The immunisation schedules for the heptavalent pneumococcal conjugated vaccine (PVC7) are as recommended by the American Academy of Pediatrics,[21] and the reader is referred to the article listed in the reference for full details. In brief, PCV7 should be administered starting at 2 months of age, every 6 to 8 weeks for a total of three doses. A booster dose is required at 12 to 15 months of age; however, if the first dose is administered at >6 to 24 months of age, only two total doses at 6 to 8 week intervals are given. No booster dose is needed if immunised after 12 months of age. Children >24 months of age require only one dose of PCV7.

Children previously immunised with PCV7 should still be given the current 23-valent pneumococcal vaccine at 2 and 5 years as recommended prior to the availability of PCV7.

Adverse effects of the PCV7 vaccine, affecting more than 10% of immunised children, include erythema at site of injection, irritability, drowsiness, restless sleep, decreased appetite, diarrhoea and fever within 48 hours of vaccination, more commonly with the second and third doses of PCV7 when given concurrently with diphtheria, tetanus, pertussis/*H. influenzae* type b conjugate vaccine.[18,22]

3. Management of the Febrile Child with Sickle Cell Anaemia

An approach to the management of the febrile child with SCA has been previously published.[23] Factors to consider requiring hospitalisation and administration of intravenous antibacterials include:

- rapid triage including the clinical impression of a physician familiar with the patient with regard to the presence of a 'toxic appearance' or meningismus
- age of the child (<6 months)
- fever of 40°C
- evidence of respiratory symptoms or pulmonary infiltrates on radiological examination
- severe haemolytic, aplastic or pain crises
- inaccessibility to immediate medical care if the child's condition worsens
- prior history of noncompliance with medications
- history of prior infections especially pneumococcal bacteraemia.

Immediate administration of intravenous antibacterials to the toxic child with SCA, after appropriate blood and urine cultures have been obtained, is of paramount importance and is often the primary life-saving effort. Lumbar punctures should be performed in the child suspected of meningitis, bearing in mind that cerebrospinal fluid pleocytosis may not be evident early in the disease.

The importance of close follow-up and diligent clinical assessment cannot be over-emphasised, whether the child is hospitalised or returns home. Outpatient treatment of selected patients with SCA can be considered in cases where the factors listed above are absent and close monitoring of the patient can be accomplished.[24,25]

3.1 Antibacterial and Antiviral Therapies

Details of all adverse effects associated with the recommended antimicrobials are beyond the scope of this article; however, as with all therapeutic regimens we must be aware of potential toxicities and adverse effects of each medication used. Acute haemolysis induced by ceftriaxone and other cephalosporins is a rare occurrence, but has been reported to have a fatal outcome.[26]

The physician must be cognizant of drug-drug interactions of clarithromycin with other drugs affected by the hepatic cytochrome P450 enzyme system such as carbamazepine, digoxin, warfarin, valproic acid and antiretrovirals.

3.1.1 Sepsis

Ceftriaxone or cefotaxime are the ideal antibacterials for most of the bacterial pathogens likely to be associated with septic episodes in SCA, including *S. pneumoniae*, *Haemophilus* spp.and *Salmonella* spp. Cephalosporin-resistance is increasing worldwide and monitoring the response to treatment is mandatory. Ceftriaxone has the longest half-life (8 to 9 hours) of the cephalosporins. However, its activity against staphylococcus is modest.[27]

3.1.2 Osteomyelitis

If symptoms of bone infection are present, nafcillin or oxacillin should be added to the treatment regimen. Aspiration of the involved joint or bone should be undertaken to determine pathogen type and sensitivities to various antimicrobials prior to institution of antibacterials, if at all possible. Salmonella osteomyelitis occurs more frequently in patients with SCA.[21] It may involve multiple sites, and swelling of the infected extremities and can mimic acute dactylitis in very young children. A 3- to 6-week course of antibacterials is usually undertaken to adequately treat the infection. However, recurrences of salmonella osteomyelitis have been observed.[28] Ciprofloxacin can be used in adolescents and adults with osteomyelitis. It should not be used in infants and pregnant women as first-line therapy. Emergence of ciprofloxacin resistance during treatment of salmonella osteomyelitis has been reported in 3 patients with SCA.[29]

3.1.3 Lung Infections

Cephalosporins have no activity against pulmonary pathogens such as *Mycoplasma* or *Chlamydia*, which often cause severe lung infections in children with SCA.[27] Therefore, if pulmonary symptoms are present, the addition of erythromycin or macrolides such as clarithromycin or azithromycin should be considered, particularly in the adolescent age group. The newer macrolides produce less gastrointestinal intolerance than erythromycin. Again, the appropriate cultures and antibody titres should be sent.

3.1.4 Yersinia enterocolitica Infection

Y. entercolitica is often encountered in patients receiving chronic blood transfusions. The organism has also been reported in cases of contaminated blood transfusions.[30,31] Hence, the child with SCA who is receiving repeated blood transfusions is at a higher risk of this infection. Common symptoms of *Y. entercolitica* infection include fever and diarrhoea, with symptoms mimicking appendicitis. This pathogen should be considered a high possible cause of infection in the febrile patient with SCA who has received repeated blood transfusions. Infection with *Y. enterocolitica* can be treated with cefotaxime or an aminoglycoside.

3.1.5 Helicobacter pylori Infection

Another cause for abdominal pain in the child with SCA is *H. pylori* gastritis. The prevalence of *H. pylori* infection in SCA is unknown, but the risk of accompanying gastrointestinal bleeding with ulcers should be considered in the patient with abdominal pain and worsening anaemia. *H. pylori* can also cause recurrent abdominal pain accompanied by vomiting. Screening for anti-*H. pylori* IgG antibody titres can be useful in determining the presence or absence of infection. Effective therapies include metronidazole, tetracycline or amoxicillin.[32] Convalescent titres should be obtained 4 to 6 months after therapy to document clearance of the infection.

3.1.6 Meningitis and Infections Caused by Multidrug-Resistant Strains of Bacteria

The rapid emergence of penicillin-resistant and multidrug-resistant *S. pneumoniae* has necessitated a re-evaluation of the approach to the management of the febrile child with SCA. β-lactamase-resistant antimicrobial combinations such as amoxicillin/clavulanate offer no advantage in the presence of penicillin-resistant pneumococci and should not be relied upon to confer any protection. It should be stressed that vancomycin should be added to the treatment regimen of a third generation cephalosporin in any child with SCA who has suspected meningitis. In the absence of meningismus or other signs of meningitis, ceftriaxone or cefotaxime should suffice for the first 24 hours. If the child improves clinically after the first 24 hours, no further changes in therapy need to be instituted. If further therapy is necessary, it should be tailored to the identification and minimum inhibitory concentrations (MICs) of the isolated pathogen. Persistence of fever past the first 24 hours or clinical deterioration warrants a further investigation for consideration of sequestered sites of infections such as abscesses, gall bladder or osteomyelitis, as well as addition of vancomycin to the regimen. However, vancomycin should not be used empirically without evidence of a high prevalence of penicillin and cephalosporin-resistant strains within the community or a clinically deteriorating status in the patient. A list of antibacterial recommendations for the treatment of serious infections in children with SCA is given in table I.

Reports of susceptibility to various antibacterials and resistant strains of organisms vary from community to community.[33] Sensitivity patterns in antimicrobial susceptibility testing for pneumococci is similar to the nomenclature used to define resistance for other bacteria such as methicillin resistant staphylococcus aureus and vancomycin resistant enterococci. All organisms with an MIC equal to or greater than that defined for the intermediate category of resistance is classified as nonsusceptible. Resistant organisms will have an MIC equal to or greater than that defined for that resistant category. Pneumococci, which are not susceptible to penicillin, cephalosporins and other antimicrobial agents are divided further into the intermediate and resistant categories based on the predicted ability of these drugs to treat pneumococcal infections effectively. The interpretive criteria for the antimicrobial susceptibilities is based on the National Committee for Clinical Laboratory Standard's guidelines.[34] Phenotypic or conventional susceptibility testing is based on either disk diffusion or broth and agar-dilation techniques. The more specific testing for susceptibility of an antimicrobial is the genotypic susceptibility testing using polymerase chain reaction (PCR) amplification of target DNA or PCR/restriction fragment length polymorphism analysis. Genotypic susceptibility testing is usually not available in most facilities. It

Table I. Recommendations for the treatment of serious infections in children with sickle cell anaemia

Condition	Treatment
Fever (> 38.8°C), no source of infection[a]	Ceftriaxone 100 mg/kg/day or cefotaxime 300 mg/kg/day
If fever persists >24 hours, add	Vancomycin 40 mg/kg/day or rifampicin (rifampin) 20 mg/kg/day
Pneumonia with x-ray changes or acute chest syndrome in child >7 years old	Ceftriaxone 100 mg/kg/day or cefotaxime 300 mg/kg/day
In child >7 years old	Cefotaxime 300 mg/kg/day + erythromycin 50 mg/kg/day
For adolescents, consider	Clarithromycin 500 mg/day or azithromycin 500mg on day 1 then 250mg × 6 days
Demonstrated or suspected osteomyelitis (modify treatment after cultures confirm aetiology)	Ceftriaxone 100 mg/kg/day or cefotaxime 300 mg/kg/day + nafcillin 150 mg/kg/day or oxacillin 150 mg/kg/day
Meningitis[b]	Ceftriaxone 100 mg/kg/day or cefotaxime 300 mg/kg/day + vancomycin 60 mg/kg/day or rifampicin (rifampin) 20 mg/kg/day

a Duration of treatment for sepsis = 7-10 days.

b Duration of treatment for meningitis = 10-14 days.

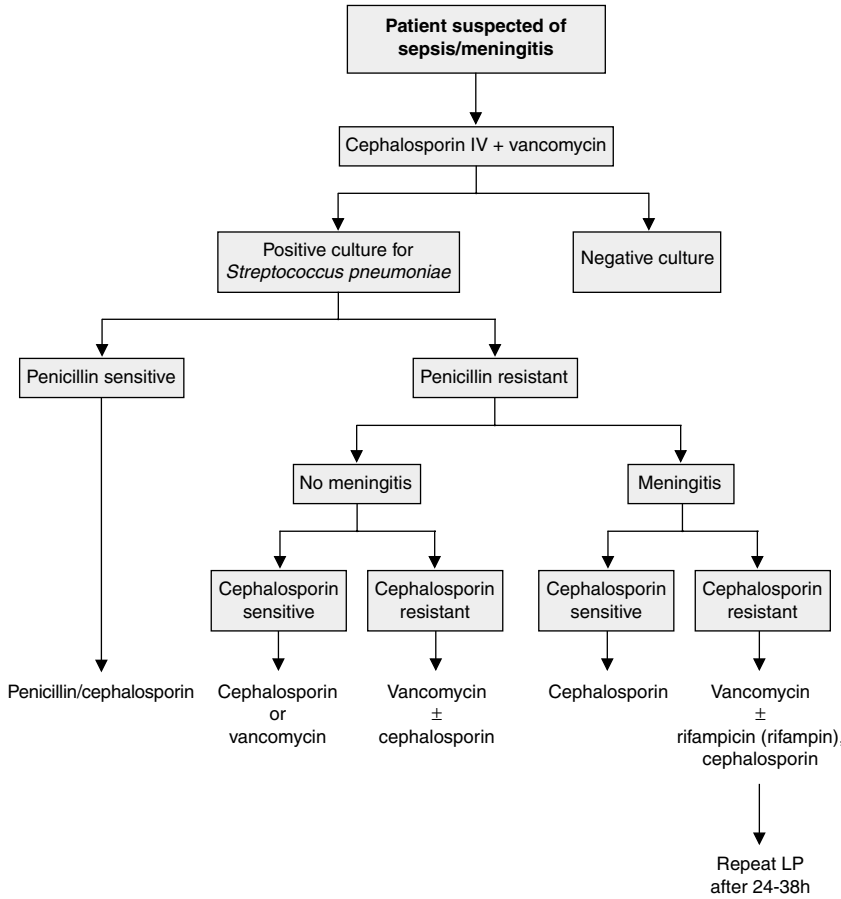

Fig. 1. Algorithm for treatment of invasive *Streptococcus pneumoniae* infection. **IV** = intravenous; **LP** = lumbar puncture.

is important for the treating physician to be aware of the MIC breakpoints for each antibacterial tested and the response for each isolate.

Sensitivity patterns of the prevalent organisms from each community and determination of the MICs are essential in using appropriate antibacterials for prophylaxis and treatment. In communities where >2% of pneumococcal isolates are penicillin-resistant, therapy for meningitis should include vancomycin + ceftriaxone/cefotaxime + rifampicin (rifampin).

Figure 1 is an algorithmic approach to treating the child with SCA suspected of having pneumococcal bacteraemia meningitis.[35]

3.1.7 Parvovirus Infections

Parvovirus infection requires supportive care and occasionally red blood cell transfusions. Specific antiviral therapy is not indicated. There is no evidence that children with SCA are more susceptible to hepatitis A, B, or C. Routine immunisations to protect against these infections and the influenzae virus should be given to each child

4. Future Directions

Emerging new antimicrobial approaches and the addition of the 7-valent vaccine to the current vaccination schedule herald an exciting period in our attempt to decrease infection-related morbidity

and mortality in children with SCA. Parents and families are taking a more proactive stance in preventative measures as well as seeking prompt medical attention. Safety and efficacy data on PCV7, following the current recommended immunisation schedule, is needed. Effective combination vaccines allowing for a decreased number of injections would also be desirable. The promise of gene therapy to eradicate SCA is yet to come; however, the future is optimistic with judicious use of current antimicrobials and continued close surveillance of evolving culpable serotypes and resistance patterns.

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