ORIGINAL ARTICLE

Bacteraemia in homozygous sickle cell disease in Africa: is pneumococcal prophylaxis justified?

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Arch Dis Child 2007;**92**:21–23. doi: 10.1136/adc.2005.088807

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Accepted 27 February 2006
Published Online First 10 March 2006

Background: The high frequency of *Streptococcus pneumoniae* as a cause of bacteraemia in homozygous sickle cell (SS) disease and its effective prevention has led to the routine use of pneumococcal prophylaxis in developed countries. The reported infrequency of this organism as a cause of bacteraemia in SS disease in Africa raises questions on the epidemiology of bacterial infection and on the need for pneumococcal prophylaxis in that continent.

Methods: A study of blood cultures in 155 Ugandan children (165 episodes) with SS disease and axillary temperatures of ⩾38°C, attending the University Teaching Hospital in Kampala (Uganda, East Africa).

Results: Positive blood cultures, obtained in 47/165 episodes, showed *Staphylococcus aureus* in 28 (60%) samples, *Haemophilus influenzae* in 9 (19%), *Staphylococcus epidermidis* in 4 (9%), and single cases of *Streptococcus viridans*, *Escherichia coli* and an unidentified Gram negative rod. *Streptococcus pneumoniae* was identified in only 3 (6%) episode.

Conclusion: The infrequent isolation of *Streptococcus pneumoniae* from febrile children with SS disease in this study and in four other studies from Nigeria raises questions on a different spectrum of bacterial causes for bacteraemia in malarial areas. There are several possible explanations for this finding, but the data cast sufficient doubt on the case for pneumococcal prophylaxis for a controlled trial on its effectiveness in that environment to seem justified. These data are necessary to determine its role in African children and to provide the evidence base for healthcare authorities in equatorial Africa.

Pneumococcal prophylaxis has been an effective intervention in the management of sickle cell (SS) disease in developed countries, reducing the frequency of invasive pneumococcal disease[1 2] and thereby increasing survival.[3] Its success is based on the high prevalence of *Streptococcus pneumoniae* as a cause of septicaemia in sickle cell disease.[4 5] The pneumococcus has also been prominent in some reports of bacteraemia in homozygous SS disease in Africa,[6 7] but more recent studies stress the dearth of *Streptococcus pneumoniae*. In Nigeria, this organism did not occur among 19 children with bacteraemia in Lagos[8] or in 181 children with bacteraemia in Kaduna,[9] and accounted for only 1 of 54 bacteraemic episodes in Benin,[10] and for 12 of 97 (12%) episodes in Ibadan.[11] In these studies the predominant organisms were *Salmonella* sp, *Staphylococcus* sp, *Klebsiella* and *Escherichia coli*. These observations raise important questions on the epidemiology of bacteraemia in SS disease in the African continent and also on the need for pneumococcal prophylaxis. In case there were factors specific to Nigeria in the four studies quoted above, a further study on the causes of bacteraemia has been performed among patients with SS disease in Uganda.

MATERIALS AND METHODS

Patients

The patients attended the Sickle Cell Clinic or the Acute Care Unit of the Department of Paediatrics & Child Health of Mulago Hospital, Kampala (Uganda, East Africa). Between 1 October 2001 and 31 January 2002, all children with SS disease <15 years of age with axillary temperatures of ⩾38°C were recruited to protocols enquiring the causes and features of septicaemia. The diagnosis of SS disease was based on a single heavy band in the position of HbS on alkaline haemoglobin electrophoresis, a positive sickle test and characteristic haematology. Newborn screening is not currently practised in Uganda, and most cases will have been ascertained by family study or symptomatic presentation. It is also difficult to define the population at risk as sick children are served by several religion-associated hospitals in the corporate area, but the Mulago Hospital remains a major source of care for sick children, especially those with SS disease.

Methods

The investigations included routine haematology, blood smear for malarial parasites (graded semiquantitatively from 1+ to 3+), blood and urine cultures in all cases, and chest radiographs where clinically indicated. Positive urine cultures were considered significant if associated with white cells on urine microscopy. Patients were routinely questioned on the use of malaria drugs or antibiotics in the 7 days preceding admission. The antibiotic sensitivity of isolated organisms was determined by standard Kirby–Bauer techniques.

Ethical issues

Consent was obtained from the Research and Ethics Committee of the Makerere University Faculty of Medicine and from the Department of Paediatrics & Child Health. Informed consent was obtained from the parents or carers of the children.

RESULTS

The study criteria were fulfilled for 165 episodes in 155 children (81 (52%) male), with a median age of 4.4 (range 0.3–14.8) years. There were 10 duplicate admissions, 4 had sterile blood cultures on both occasions (interval between admissions, 20–68 days), 4 had sterile cultures followed by culture of *Staphylococcus aureus* (interval between admissions, 28–98 days), 1 had a sterile culture followed by isolation of *Haemophilus influenzae* (interval between admissions, 27 days), and another had isolation of *Streptococcus pneumoniae* followed by isolation of *H influenzae* (interval between admissions, 44 days). The principal diagnoses, summarised in table 1, show that

Table 1 Summary of clinical and laboratory findings in 165 febrile episodes

	Blood cultures			Urine cultures					
	Staphylococcus aureus	*Haemophilus influenzae*	*Streptococcus pneumoniae*	Others	*Escherichia coli*	Others	Malaria	No other findings	Total
Febrile only	22	3	2	4	–	–	3	76	110
Acute chest syndrome	5+ (1)*	5	1	3	3	1+ (1)*	–	28	47
Urinary tract infection	–	1†	–	–	5+ (1)†	2	–	–	8
Total	28	9	3	7	8+ (1)	3+ (1)	3	104	165

*Associated with urinary tract infection (*Klebsiella pneumoniae*, cells in urine).
†Associated with urinary tract infection (*Escherichia coli*, cells in urine).

bacteraemia occurred in 47 (28%) children, urinary tract infections in 11 (7%), and that an additional two patients with urinary tract infection had positive blood cultures with a different organism. Three patients were considered to have malaria on the basis of 2+ malarial parasites, although a further 13 patients had 1+ malarial parasites, which is of doubtful relevance as it is not uncommon in clinically well patients. A total of 47 patients had radiological evidence of acute chest syndrome, 15 with positive blood cultures, 4 with evidence of urinary tract infection and 28 without positive cultures. In 76 episodes, no bacterial cause could be found.

Clinical measurement of spleen size was available in 164 episodes, being impalpable in 105 (64%), 2–4 cm in 39 (24%), 5–8 cm in 14 (9%) and 9–10 cm in 6 (4%). There was no clear relationship between splenomegaly and positive blood cultures; in the 27 episodes with *Staphylococcus aureus*, the spleen was impalpable in 16 and ranged from 3 to 10 cm in 11 episodes; in the 9 episodes with *H influenzae*, the spleen was impalpable in 4 and ranged between 2 and 5 cm in 5; in the 3 episodes with *Streptococcus pneumoniae*, the spleen was impalpable in one and measured 4 cm in the other two.

The organisms isolated from the 47 bacteraemias (table 2) were *Staphylococcus aureus* in 28.2 (60%), *H influenzae* in 8.93 (19%) and *Streptococcus pneumoniae* in only 3 (6%) cases. In one of the cases with *Streptococcus pneumoniae*, the subsequent isolation of *H influenzae* may seem surprising although there is evidence that a subgroup of patients may be prone to recurrent bacteraemias.[12] The median age of onset seemed earlier for *H influenzae* and *Streptococcus pneumoniae,* but the difference did not reach statistical significance ($p>0.05$). All three patients with *Streptococcus pneumoniae* survived.

The use of antibiotics before the febrile illness was admitted in 41 (25%) febrile episodes and in 13 (28%) children with bacteraemia. It was most commonly amoxycillin (n = 11) or cotrimoxazole (n = 7); the antibiotic was unspecified in 11 and only 3 admitted to prior use of penicillin. Of the three pneumococcal isolations, none had received pneumococcal vaccine, and two had taken prior antibiotics (chloramphenicol in one, erythromycin in one); two of the three organisms showed resistance to penicillin.

DISCUSSION

There are many limitations to this study, illustrating the difficulties in performing clinical research with limited clinical, medical and social infrastructure, characterising the conditions in much of equatorial Africa. The Sickle Cell Clinic at Mulago Hospital has very limited resources and has not yet been able to implement regular review of patients in the steady state, vital to establishing proper prospective management and parental education. Patients frequently attend only when seriously ill, which inevitably biases the patients presenting to clinical facilities. There is no programme yet for newborn screening, and the denominator for the current patient group is unknown because of the social, medical and geographical factors affecting attendance. Special financial arrangements had to be made for this study so that the cost of blood culture and of chest radiographs was not contingent on the family's ability to pay. All of these considerations limit the ability to perform clinical research in much of Africa.

Despite these limitations, this is the fifth study from equatorial Africa showing the paucity of *Streptococcus pneumoniae* as a cause of bacteraemia in patients with SS disease. Other studies noted the predominance of *Klebsiella* sp and *Staphylococcus albus*,[8] *Klebsiella* sp and *Salmonella* sp,[10] *Klebsiella* sp and *Staphylococcus aureus*,[11] and *Staphylococcus aureus* and *Salmonella* sp.[9] In this study, *Staphylococcus aureus* accounted for 60% and *H influenzae* for 19% of patients with SS disease. These observations may seem to be of only regional significance, but they raise important questions on the mechanisms of susceptibility to bacterial infection and on the relevance of pneumococcal prophylaxis in the African environment. It could be argued that the predominance of *Staphylococcus aureus*, *Salmonella* sp and *Klebsiella* sp simply reflects high levels of carriage of these organisms in that environment,[13] and that these obscure an underlying susceptibility to *Streptococcus pneumoniae*. It has also been argued that the apparent lack of susceptibility to *Streptococcus pneumoniae* is so conceptually unlikely that other explanations must be sought, such as the death of affected children before receiving medical attention or the widespread use of over-the-counter antibiotics. There are also suggestions[9] that malaria, with its associated splenomegaly, may favour the persistence of splenic function during the critical period of

Table 2 Features of bacterial isolate among 47 patients with positive blood cultures

Organism	n (%)	Median age (range), years	Events <3 years, n (%)
Staphylococcus aureus	28 (60)	3.3 (0.7–14.8)	11 (39)
Haemophilus influenzae	9 (19)	1.4 (1.0–13.1)	5 (56)
Staphylococcus epidermis	4 (9)	4.4 (1.3–11.0)	1
Streptococcus pneumoniae	3 (6)	1.3 (1.0–2.1)	3 (100)
Streptococcus viridans	1	4.2	0
Escherichia coli	1	4.0	0
Gram negative rod	1	9.0	0

What is already known on this topic

- Septicaemia in patients with sickle cell disease in non-malarial areas is usually caused by *Streptococcus pneumoniae*.
- Its incidence has been reduced by pneumococcal prophylaxis.

What this study adds

- African studies are consistent in showing a dearth of this organism, raising doubts on the necessity of pneumococcal prophylaxis.
- A trial of pneumococcal prophylaxis is recommended in Africa to convince healthcare planners of the need for this programme and the associated expense.

susceptibility[5] similar to that described in Eastern Saudi Arabia, where high levels of fetal haemoglobin may have a similar beneficial effect.[14 15] Pneumococcal prophylaxis in western (non-malarial) countries is based on firm evidence of the high prevalence of *Streptococcus pneumoniae* as a cause of bacteraemia and of penicillin in its prevention. The available data from the African continent fulfil neither of these criteria. Are we to ignore these data and persist with conceptions that interventions developed elsewhere must be appropriate, or is this a situation where clinical trials are necessary? A trial of pneumococcal prophylaxis in that environment must have a high priority if African governments are to be persuaded of its necessity. Financial and infrastructure restraints of many institutions in Africa may limit facilities for investigation such as blood culture, but the simple demonstration that children randomised to pneumococcal prophylaxis have fewer complications or survive better would effectively answer this question. This problem requires a resolution to ensure that African governments do not spend scarce resources on inappropriate interventions.

This also raises broader issues on the effect of malaria on the natural history of SS disease. There is consensus that malaria has a profound effect on the outcome of SS disease, contributing to death directly from malaria and also from sickle-related complications. That SS disease in an African environment may behave differently from that in non-malarial areas is already suggested by the dearth of *Streptococcus pneumoniae* as a cause of bacteraemia. Parental education in the early diagnosis of acute splenic sequestration,[16] shown to improve survival in SS disease in non-malarial areas, may also be compromised by the effect of malaria on the natural history of splenomegaly in SS disease. These observations suggest that the automatic transfer of interventions from non-malarial areas, without assessing the local situation, may be neither relevant nor justified. The interaction of malaria and SS disease is poorly understood and there is an urgent need to document this and the natural history of SS disease in a malarial environment. As shown elsewhere, this is most appropriately performed in a cohort study following newborn diagnosis; this may be a long-term investment in countries such as Jamaica, where 15-year survival in SS disease is 84%,[3] but with the high early mortality anticipated in Africa, important information would probably be gained over the first 3–5 years. African colleagues and funding agencies should be persuaded that this is an urgent necessity for African children with SS disease.

ACKNOWLEDGEMENTS

We thank the Department of Microbiology for blood culture results and Professor GR and Mrs BE Serjeant for funding the project.

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Competing interests: None declared.

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