ORIGINAL ARTICLE

Bacteraemia due to *Staphylococcus aureus*

S Ladhani, O S Konana, S Mwarumba, M C English

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See end of article for
authors' affiliationsCorrespondence to:
Dr S Ladhani, PO Box 230,
Kilifi, Kenya; drshamez@
aol.com

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Aims: To describe the clinical features and outcome of bacteraemia due to *Staphylococcus aureus* in children admitted to a rural Kenyan hospital.**Methods:** Retrospective case review of all children with a positive blood culture for *S aureus* admitted to Kilifi District Hospital, Kenya, between January 1996 and December 2001.**Results:** Ninety seven children (median age 17 months, range 1 day to 12 years; 46 male) with bacteraemia due to *S aureus* were identified, accounting for 5% of all positive blood cultures; 10 were considered to be nosocomially acquired. A focus that was clinically consistent with staphylococcal infection was identified in 52 cases; of these, 88% had multiple foci. Children with a focus were likely to be older, present later, and have a longer duration of hospital stay. Most children in this group (90%) received intravenous cloxacillin on admission in contrast to none of those without a focus. In the former group, mortality was only 6% compared to 47% among those without a focus; 10/13 neonates without an apparent staphylococcal focus died compared to none of the 11 with a focus. Eight of the 10 neonates in the former group died within 48 hours of admission, before empirical antibiotics could be changed to include cloxacillin.**Conclusions:** Children most at risk of death associated with bacteraemia due to *S aureus* are least likely to have clinical features traditionally associated with this infection.

Despite the development of effective antibiotics and improvements in hygiene, *Staphylococcus aureus* remains a major human pathogen.¹ *S aureus* produces disease in two main ways. Production of toxins leads to specific diseases such as staphylococcal scalded skin syndrome, gastroenteritis, and toxic shock syndrome, while direct tissue invasion causes localised folliculitis, abscesses, cellulitis, pyomyositis, osteomyelitis, and septic arthritis.² Severe infection can present as overt septicaemia occasionally followed by disseminated secondary infection, including pneumonia, endocarditis, and meningococcalitis.^{3 4}

Bacteraemia due to *S aureus* occurs in all age groups and carries a significant mortality of 20–35%, which has been consistent for the past few decades.^{4–13} However, most of these studies have been performed in adults and little is known about bloodstream infections due to *S aureus* in children,¹³ particularly in developing countries.¹⁴ At Kilifi District Hospital, *S aureus* accounts for around 5% of all organisms isolated from blood cultures in children, and bacteraemia is associated with a significant mortality (J Berkley, personal communication). We were, therefore, interested in describing the clinical features and outcome of *S aureus* bacteraemia in our paediatric patients.

METHODS

Kilifi District Hospital is located on the Kenyan coast in a mainly rural, malaria endemic region with two seasonal peaks of transmission a year. The paediatric in-patient service provides a 36 bed general paediatric ward and a five bed high dependency unit for around 5000 children a year. The characteristics of the population served and malaria transmission have been described previously.¹⁵ The microbiological database at the hospital was examined to identify all positive blood cultures for *S aureus* between January 1996 and December 2001. Between 1996 and mid-1998, blood cultures were taken on admission at the discretion of the attending physician, and thereafter on all children with a history of fever or observed fever as part of a comprehensive study. There was no difference in the number of positive *S aureus* isolates per

year before and after mid-1998. Bacteraemia was considered to be community acquired if there was a positive blood culture for *S aureus* from a sample taken aseptically at or within 48 hours of admission or when there was a staphylococcal focus of infection at admission.^{5 9 16} Nosocomial infection was defined as isolation of *S aureus* from blood cultures at least 48 hours after hospital admission with a negative blood culture on admission. Because heights were not routinely measured, children were considered to be severely malnourished if their weight for age was less than 60% of National Center for Health statistic median, as determined using the computer program EPINUT (EPIinfo 6, Centers for Disease Control and Prevention, Atlanta, USA; www.cdc.gov/epiinfo).

Before 1998, blood was inoculated into a single bottle of brain-heart infusion broth, incubated for seven days, and examined daily for turbidity, haemolysis, or other evidence of growth. After 1998, blood cultures were processed utilising a BACTEC 9050 system instrument (Becton Dickinson, New Jersey, USA). Samples indicated as positive using the BACTEC system or by inspection prior to this technique were further processed utilising standard culture media and routine microbiological techniques. API biochemical galleries (Biomerieux, Louvres, France) and/or serology were used to confirm suspected pathogens. Antibiotic sensitivities were performed using the Etest assay (AB Biodisk, Sweden).

Current policy for antibiotic treatment in children admitted to Kilifi District Hospital includes cloxacillin for children clinically suspected to have a staphylococcal infection, along with surgical drainage of localised infection as appropriate. Neonatal septicaemia and children with protein-calorie malnutrition are treated empirically with benzylpenicillin and gentamicin, until blood culture results become available. Children with pneumonia are diagnosed clinically and treated according to the World Health Organisation guidelines, with penicillin for severe pneumonia or chloramphenicol for very severe pneumonia, as per local protocol.^{17 18} Children with gastroenteritis, defined as three or more episodes of diarrhoea and vomiting in a 24 hour period, did not receive antibiotics on admission unless the stool was

blood stained (when they received nalidixic acid or chloramphenicol), or subsequent cultures revealed a significant pathogen. Individual data for human immunodeficiency virus infection status were not available, but a recent anonymous, unlinked survey of children admitted to our paediatric ward in the year 1999/2000 estimated an overall prevalence of 7% (J Berkley, unpublished data).

A predefined questionnaire was used to extract all relevant information for each patient, including: (a) patient details, including age, sex, and weight; (b) presenting features; (c) clinical findings, including presence of any focus of infection consistent with *S aureus* infection; (d) results of any haematological, biochemical, microbiological, and radiological investigations; (e) antimicrobial susceptibility of *S aureus* isolated from blood cultures; (f) treatment; (g) duration of in-patient stay; and (h) outcome. The data were entered into Microsoft Visual Foxpro (version 6.0) and statistical analysis was performed using Stata 6.0 for Windows. The white cell count was log transformed to achieve a normal distribution before analysis. Other data that do not follow a normal distribution are presented as medians with their respective interquartile ranges. Groups were compared with the χ^2 test or Fisher's exact test for proportions, and the *t* test for continuous variables. A logistic regression model was constructed to explore the independent effects of variables apparently associated with death in univariate analyses.

RESULTS

Approximately 35 000 blood cultures were taken during the six year period and 2100 (6%) yielded significant organisms (J Berkley, unpublished data). *S aureus* was isolated from blood cultures of 106 (5%) children. Five children with polymicrobial infection (two *Escherichia coli*, one *Salmonella* sp., one *Enterobacter* sp., and one *Klebsiella* sp.) were excluded from the study. In another four excluded cases, the principal diagnosis was considered to be severe malaria, the positive blood culture result either representing contamination or true dual pathology. The remaining 97 children were included in the study. Their median age was 17 months (range 1 day to 12 years) (fig 1); 46 were male, and 10 were considered to have hospital acquired infection.

A focus that was clinically consistent with staphylococcal infection was identified in 52/97 (53.6%) cases on admission; of these, 88% had multiple foci. The most common focus was a superficial abscess (42.3%), followed by cellulitis (32.7%), osteomyelitis (25.0%), pyomyositis (15.4%), oomphalitis (7.7%), empyema (5.8%), septic arthritis (5.8%), staphylococcal scalded skin syndrome (3.8%), infected scabies (3.8%), lymphadenitis (1.9%), and infected burns (1.9%). Children presenting without a focus commonly associated with

Figure 1 Age range of children presenting with bacteraemia due to *S aureus*.

staphylococcal disease were more likely to have malnutrition and present with clinical features of pneumonia and gastroenteritis (table 1), but neurological symptoms (two children in each group) and neonatal septicaemia (13 v 11 neonates) were equally common in children presenting with a staphylococcal focus of infection as in those without a focus, respectively. During the six year study period, there were only three radiologically confirmed and culture proven cases of staphylococcal pneumonia with empyema. All three had superficial abscesses and received intravenous cloxacillin on admission, following chest drain insertion.

Children with a focus were more likely to be older, present later, and have a longer duration of hospital stay (table 1). In this group, 13 children (of whom 10 were >5 years old) presented with osteomyelitis (eight of them following a radiologically confirmed traumatic fracture 1–4 weeks previously), usually associated with wound abscesses and cellulitis, as well as septic arthritis in three cases. These children required prolonged admission for intravenous antibiotics for 4–6 weeks together with orthopaedic surgery for treating the fracture.

Of the 97 staphylococcal strains isolated, 92% were resistant to penicillin, 4% to chloramphenicol, 1% to cloxacillin, and 1% to gentamicin. The 9 year old child with cloxacillin resistant but chloramphenicol sensitive *S aureus* bacteraemia was severely malnourished, had no identifiable staphylococcal focus, presented with symptoms of very severe pneumonia, and was treated with chloramphenicol on admission and improved. Most children with a focus (90.4%) received intravenous cloxacillin on admission in contrast to none in those without a focus. In the former group, mortality was only 5.8% compared to 46.7% among those without a focus (odds ratio 14.3; 95% CI 3.6 to 79.8) (table 1). Mortality was not different between the two groups for pneumonia (6/17 with a focus v 1/6, $\chi^2 = 1.8$, *p* = 0.36), gastroenteritis (5/12 v 1/5, $\chi^2 = 0.73$, *p* = 0.60), or neurological symptoms (none died).

Neonates (aged 28 days or less) accounted for 24/97 (25%) of children with bacteraemia due to *S aureus*. The 11 neonates with a focus of infection were older (median age 12 (range 2–27) days v 5 (2–21) days, *p* = 0.02) and had a longer duration of illness before presentation (median 4 (range 1–7) days v 2 (1–5) days, *p* = 0.04). However, there was no significant difference in admission weight, haemoglobin level, or white cell count. Overall, neonates had a much higher mortality (10/24, 42%) compared to older infants and children (14/73, 19%; $\chi^2 = 4.91$; *p* = 0.027); all neonatal deaths occurred in those

Table 1 Comparison of children with a known *S aureus* focus and unknown focus

	Known focus (n = 52)	Unknown focus (n = 45)	p value
Duration of illness (days)*	4.5 (3–7)	3 (2–5)	0.014
Age at presentation (mth)*	32.5 (5.5–78.5)	10 (0.5–26)	0.0055
Duration of in-patient stay (days)*	11.5 (7.5–26.0)	5.0 (2.0–12.0)†	0.0001
Malnutrition (excluding neonates)	6 (11.5%)	16 (35.6%)	0.0048
Pneumonia	9 (17.3%)	17 (37.8%)	0.038
Gastroenteritis	5 (9.6%)	12 (26.7%)	0.034
Admission haemoglobin (g/l)	97 (27)	104 (32)	0.29
Admission white cell ($\times 10^9/l$)	15.3 (1.7)	15.3 (1.8)	0.97
Nosocomial acquisition	5 (9.6%)	5 (11.1%)	1.00
Malaria slide positive	6 (11.5%)	4 (8.9%)	0.75
Male	24 (46.2%)	21 (46.7%)	0.96
Mortality	3 (5.8%)	21 (46.7%)	<0.0001

Haemoglobin values are given as mean (SD); white cell counts given as geometric mean (SD).

*Denotes values given as median (interquartile range).

†This group includes 13 children who died within 48 hours of admission.

without a staphylococcal focus (10/13 without a focus died compared to 0/11 with a focus, $\chi^2 = 14.5$, $p = 0.0001$). Eight of the 10 neonates without a focus who died, did so within 48 hours of admission (six within 24 hours), before empiric antibiotic could be changed to cloxacillin. Among the 24 neonates with *S aureus* bacteraemia, mortality was associated with absence of a focus of infection (10/13 v 0/11 with a focus, $\chi^2 = 14.5$, $p < 0.0001$), younger age at presentation (median 5 days (range 1–9) v 13.5 (2–7), $p = 0.004$) and shorter duration of illness (median 1.5 days (range 1–5) v 3 (1–7), $p = 0.03$), but not with mean weight, admission haemoglobin, or the geometric mean white cell count ($p > 0.10$). However, even after excluding neonates, children without a focus of infection had a higher mortality (11/32) compared to those with a focus (3/41, $\chi^2 = 8.49$, $p = 0.004$).

Table 2 lists the risk factors for mortality associated with *S aureus* bacteraemia. Children with nosocomially acquired *S aureus* bacteraemia ($n = 10$) were excluded from the analysis because they were considered to be a distinct group with different risk factors, compared to those with community acquired *S aureus* infection. Children between the ages of 1–11 months and 12–60 months were grouped together for analysis because they had similar proportions of children with a focus of infection (6/17 v 12/23; $\chi^2 = 1.13$, $p = 0.29$) and mortality (4/17 v 6/23, $\chi^2 = 0.07$, $p = 0.79$). Absence of a focus of infection (and, therefore, failure to receive intravenous cloxacillin on admission), younger age, and malnutrition were all associated with mortality (table 2) in the univariate analysis. In a multivariate logistic regression model using three categories for age (neonates, 1–60 months, and >60 months as the index group), presence or absence of a focus of infection (which may be related to receiving cloxacillin on admission), and malnutrition, only absence of a focus (OR 16.8; 95% CI 3.23 to 86.4) and younger age (OR 3.7; 95% CI 1.3 to 10.9) remained significantly associated with mortality.

DISCUSSION

We have reported one of the largest paediatric series on blood stream infections due to *S aureus* in developing countries. Almost half the cases did not present with a focus that was clinically consistent with staphylococcal infection. As a consequence, this group did not receive specific antistaphylococcal antibiotics and had a much higher mortality rate compared to children who presented with a staphylococcal focus of infection and received cloxacillin on admission. Adults studies have consistently shown that inappropriate initial antibiotic therapy for bacteraemia due to *S aureus* is an important risk factor for

mortality,^{5–8} and this may at least in part result from an absence of a staphylococcal focus on admission.⁵

In our study population, *S aureus* accounted for 5% of all organisms isolated from blood cultures during the six year period, which is comparable to previously reported epidemiological studies,^{1,2} although one Nigerian study reported a 30.5% blood culture isolation rate for *S aureus* among 920 adult and paediatric patients over an eight year period.¹⁹ Because *S aureus* is a common skin commensal, it is possible that the organism is just a contaminant in some cases. Several different clinical and laboratory criteria have been proposed for distinguishing between pathogenic infection and contamination. Using a modification of one used in adult studies,^{5,9} and defining *S aureus* septicaemia as a positive blood culture with pure growth of *S aureus* and at least three of the following: fever >38.5°C, rigors, age specific tachycardia, leucocytosis, and hypotension,²⁰ all 97 children fulfilled the criteria for septicaemia.

Unlike most adult studies where nosocomial acquisition is more common,^{6,9} almost 90% of our patients had community acquired bacteraemia. A focus of *S aureus* infection was identified in around half the cases, which is lower than previous adult studies reporting a focus in 78% of 281 cases,⁵ 66% of 107 cases,⁸ and 63% of 105 cases.¹⁰ Those with a focus were more likely to be older, present later, and have a longer duration of hospital stay in our study. There are two reasons that may explain this observation. Firstly, a significant proportion of children with a focus presented with osteomyelitis associated with a traumatic fracture, and these children required prolonged hospitalisation for intravenous antibiotics. Secondly, 10 of 13 neonates without a focus died within 48 hours of admission, and would contribute to a shorter duration of stay among those without a focus.

Bloodstream infections due to *S aureus* have been described in children who present with no apparent focus of infection on examination. One Nigerian study found that 15.8% of 60 children diagnosed with septicaemia on admission without any identifiable focus had *S aureus* isolated from blood cultures.²¹ Similarly, another Indian study looking at 100 febrile children aged 1 month to 3 years with no focus of infection found *S aureus* to be the most common bacterial isolate from blood cultures.²² *S aureus* is also one of the most frequently isolated organisms in children at high risk of infections, such as sickle cell disease and protein-calorie malnutrition.^{23,24}

In our study, children without a staphylococcal focus presented mainly with pneumonia and gastroenteritis. It is not routine practice to perform chest radiographs in patients

Table 2 Mortality among 87 children with community acquired bacteraemia due to *S aureus*

Parameter	Alive (n = 66)	Dead (n = 21)		Significance
Age at admission				
Neonates	12/22	10/22	χ^2 for trend = 10.9	0.001
Age 1–60 mth	30/40	10/40		
Age >60 mth	24/25	1/25		
Absence of focus of infection	21 (31.8%)	19 (90.5%)	OR = 20.4 (4.0 to 140)	<<0.0001
Malnutrition (excluding neonates)	9/54 (16.7%)	5/11 (45.5%)	OR = 4.17 (0.80 to 20.3)	0.034
Pneumonia	18 (27.3%)	7 (33.3%)	OR = 1.33 (0.41 to 4.30)	0.59
Gastroenteritis	9 (13.6%)	4 (19.0%)	OR = 1.49 (0.33 to 6.29)	0.37
Duration of illness*	4.0 (3–7)	3.0 (1–5)	–	0.074
Haemoglobin (g/l)	98 (28)	113 (38)	–	0.054
White cell count ($\times 10^9$ /l)	15.3 (1.7)	14.6 (2.0)	–	0.73
Positive malaria parasite slide	8 (12.1%)	1 (4.8%)	OR = 0.36 (0.02 to 3.21)	0.33
Antibiotics on admission				
Penicillin + gentamicin	10 (15.2%)	19 (90.5%)	OR = 53.2 (9.49 to 349.5)	<<0.0001
Chloramphenicol	10 (15.2%)	2 (9.5%)	OR = 0.59 (0.08 to 3.30)	0.72
Cloxacillin	46 (69.7%)	0 (0%)	OR = 0.00 (0.00 to 0.11)	<<0.0001

Haemoglobin values are given as mean (SD); white cell counts as geometric mean (SD).

*Denotes values given as median (interquartile range).

suspected with pneumonia in resource-poor settings. The diagnosis, therefore, relies on clinical criteria, and it is possible that in some cases either the diagnosis was inaccurate or the pneumonia was not due to *S aureus*. Similarly, although *S aureus* can cause gastroenteritis,² diagnostic kits for testing stool specimens for staphylococcal enterotoxins are not available at our hospital. Endocarditis is also a known complication of *S aureus* bacteraemia in adults^{4 5 9 10 12} and children.^{25 26} In one study, 4/11 (36%) of children with staphylococcal septicaemia who underwent echocardiography had clinically silent endocarditis, with pericarditis diagnosed in a further two children.²⁶ Several adult studies have shown that staphylococcal endocarditis is much more common in those without a focus and carries a higher mortality.^{4 5 9 10 12} One study reported that 24 of 26 cases of endocarditis in adults with *S aureus* bacteraemia occurred in those without an identifiable focus.¹⁰ Unfortunately, echocardiography facilities are not available at our local hospital. It is, therefore, possible that some of the children, particularly those without a focus, may have had endocarditis, which may have contributed to the higher mortality observed in this group.

It is reassuring that methicillin resistance is rare in our population, accounting for only 1% of all isolates. This rate is comparable to 3% methicillin resistance reported in a previous study involving 121 isolates from adults with human immunodeficiency virus seropositivity from the same area,²⁹ but is much lower when compared to neighbouring regions, where methicillin resistance accounted for 30–60% of all staphylococcal isolates.^{30–32}

The overall mortality in our study was 24% and the logistic regression model identified two main independent risk factors—absence of a staphylococcal focus and younger age. The observation that neonates accounted for a quarter of all cases supports previous reports suggesting that this group may be at higher risk of developing *S aureus* septicaemia.^{13 27 28} In two different Nigerian studies, *S aureus* accounted for around a third of all organisms isolated from blood cultures of neonates with septicaemia.^{27 28} In our patients, 11 neonates presented with a staphylococcal focus. Four had documented oomphalitis on admission; the others had pustular skin infections (n = 2), localised abscesses (n = 2), mastitis (n = 2), and staphylococcal scalded skin syndrome (n = 1). Neonates, almost invariably those without a staphylococcal focus on admission, had a much higher mortality compared to older children, and most died within 48 hours of admission before antibiotics could be changed to include cloxacillin. These findings question whether empiric treatment for neonatal septicaemia should include a more specific anti-staphylococcal antibiotic, and emphasises the importance of local microbiological surveillance for developing local antimicrobial policies. Indeed, empiric treatment with cloxacillin should be considered for all children with septicaemia, since children in all age groups had a higher mortality in our study. Similar recommendations have been proposed in the past for adults suspected with septicaemia.⁵

Conclusions

Bacteraemia due to *S aureus* in children continues to carry a significant mortality. Almost half the patients in our study presented without a staphylococcal focus of infection. This group, particularly neonates, had a 14-fold increase in mortality, which may be related to not receiving a specific antistaphylococcal antibiotic on admission. Further studies that consider the cost and benefit of new empiric regimes are required to determine whether specific antistaphylococcal antibiotics should be included in empirical treatment of children, particularly neonates, with septicaemia in developing countries.

Authors' affiliations

S Ladhani, O S Konana, S Mwarumba, M C English, Centre for Geographic Medicine Research, Coast, KEMRI, and Wellcome Trust Laboratories, Kenya

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