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# Antibiotic treatment duration and prevention of complications in neonatal *Staphylococcus aureus* bacteraemia

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SUMMARY

***Background:*** In adults with *Staphylococcus aureus* bacteraemia, short duration of effective antibiotic treatment is associated with increased risk of complications and recurrence. The optimum duration of treatment for neonates is unknown and practice varies widely.

***Aim:*** To relate the duration of treatment of neonatal *S. aureus* bacteraemia to prevention of complications and recurrence.

***Methods:*** Retrospective cohort study of confirmed *S. aureus* bacteraemia occurring over a 10 year period in two large tertiary neonatal units. Neonatal patients developing confirmed *S. aureus* bacteraemia between birth and discharge from the neonatal unit were identified from microbiology department records. Clinical details obtained from case notes included demographics, duration of antibiotics and clinical outcomes. Recurrence was determined from laboratory and clinical records. Adverse outcomes were related to duration of antibiotic therapy.

***Findings:*** A total of 90 infants had *S. aureus* bacteraemia, of which six were meticillin-resistant *S. aureus* (7%). Median gestation was 27 weeks (range: 23–41), birth weight 846 g (434–3840) and postnatal age 16 days (0–116). Adverse outcomes were found in 44%, with death in 8%. Median duration of appropriate antibiotics was 19 days (range: 0–54). There were no cases of recurrent bacteraemia after finishing antibiotics. There was no relationship between antibiotic duration and complications.

***Conclusion:*** Neonatal *S. aureus* bacteraemia mainly affected preterm neonates and had a significant morbidity and mortality. Recurrent bacteraemia was rare, irrespective of treatment duration. For neonatal unit patients with *S. aureus* bacteraemia, antibiotic therapy for 14 days in uncomplicated cases may be sufficient to prevent recurrence, with longer treatment justified if there is inadequate source control.



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## Introduction

Neonatal *Staphylococcus aureus* bacteraemia and sepsis remain important clinical problems. Recent surveillance reported *S. aureus* as second only to coagulase-negative staphylococcus as the cause of neonatal bacteraemia in the UK, and device-associated neonatal bacteraemia in the USA.[1,2] Of these isolates, 8% in the UK and 33% in the USA were meticillin-resistant (MRSA). A review of community-acquired neonatal sepsis in developing countries found *S. aureus* to be the most prevalent pathogen isolated.[3]

In adults, *S. aureus* bacteraemia is frequently associated with metastatic disease, affecting heart valves, joints, kidneys, and central nervous system, contributing to morbidity and acting as a reservoir for recurrent disease.[4] Recurrence is high if central lines are not removed.[5] Some studies have demonstrated links between shorter treatment duration and recurrent disease, but others have not.[5,6] A recent review highlighted the lack of clear evidence for most aspects of *S. aureus* bacteraemia management in adults, with only one randomized trial directly addressing antibiotic therapy duration.[7,8] Their only clear conclusions were that infective foci must be identified and removed if possible, and that long-term antimicrobial therapy is required for persistent bacteraemia or an irremovable focus.

Recommended duration of therapy in adults depends on whether disease is complicated or uncomplicated. Complicated disease is defined by a positive follow-up blood culture at 48–96 h, community-acquired infection, persistent fever at 72 h or skin lesions suggesting systemic infection. Uncomplicated disease is indicated by catheter-associated infection with removal of the catheter, negative follow-up blood culture, defervescence within 72 h, normal transoesophageal echocardiogram, no prosthetic material in joints or intravascular space, and no symptoms suggesting metastatic infection.[9]

Recent guidelines have been produced for treating MRSA bacteraemia in adults and children. Guidance from the UK recommended $\geq$14 days of treatment for uncomplicated MRSA bacteraemia and longer for complicated disease, with no specific guidance for children.[10] The Infectious Diseases Society of America recommended two weeks of treatment for uncomplicated MRSA bacteraemia and four to six weeks for complicated adult cases. In children they recommended intravenous vancomycin for two to six weeks with MRSA bacteraemia or proven endocarditis, with no specific recommendations for therapy duration in neonates.[11]

Prevention of recurrence is an important element within strategies to reduce the burden of hospital-acquired *S. aureus* infection in adults. There is little known about the burden of recurrent disease in neonatal unit populations or how it is influenced by antibiotic treatment duration. Several aspects of immune function in neonates explain their susceptibility to *S. aureus* infection. They rely on maternal IgG transferred across the placenta, which may be deficient if they are delivered prematurely.[12] Neonates have reduced complement function, neutrophil chemotaxis and bacterial killing, suggesting that they may need longer therapy to prevent recurrence.[13,14] This study aims to examine outcomes following *S. aureus* bacteraemia in neonates, relating the duration of antibiotic treatment to complications and recurrence.

## Methods

### Procedures

Laboratory microbiology databases were used to identify all cases of *S. aureus* bacteraemia in admissions to two large neonatal units over a 10-year period (2001–2010). When positive *S. aureus* cultures were taken, all infants were inpatients in the neonatal unit of either the Homerton Hospital (48 cases) or the Royal London Hospital (42 cases) in East London, UK. These provide neonatal care for their local populations and also take external medical and surgical referrals as tertiary neonatal intensive care units. Neither unit had standard guidance on duration of therapy for *S. aureus* bacteraemia and clinicians made decisions on an individual basis in conjunction with medical microbiologists.

Bacteraemia was defined by the isolation of *S. aureus* from a blood culture, taken from a peripheral vein. The units practised standard aseptic procedures for blood culture collection with skin preparation using a 70% isopropyl alcohol swab. Blood cultures were processed in accredited laboratories using standard operating procedures and automated systems. During this study, *S. aureus* isolates were not routinely tested for toxins. Clinical sepsis was defined as bacteraemia treated with antibiotics with clinical signs or a raised C-reactive protein (CRP). The study received approval from the clinical governance committees of both institutions (Reference nos.: 614/670 Homerton, 081-11 Royal London).

Clinical details were extracted from medical records, to identify risk factors at the time of infection and outcomes. Prior specified adverse outcomes were death, bacterial endocarditis, osteomyelitis, renal abscess, meningitis, brain abscess, pneumatocoele, duration of oxygen requirement, and recurrent *S. aureus* infection either during admission or during paediatric admission in the first year of life. Other non-specified complications and adverse outcomes were recorded.

Appropriate antibiotics were defined as those to which the organism was identified as susceptible by standard methods (British Society for Antimicrobial Chemotherapy, Birmingham, UK). For orally absorbable drugs such as flucloxacillin, duration of appropriate antibiotics was the total of intravenous and oral.

Recurrence was defined as any clinical illness with isolation of *S. aureus* after stopping appropriate antibiotic therapy, recorded in the hospital or laboratory record during the first year of life, including both bacteraemia and localized disease. Breakthrough disease was defined as a positive *S. aureus* culture during the primary antibiotic course. Classical *S. aureus* disease was defined as abscess, osteomyelitis, impetigo, or scalded skin syndrome. Complicated disease was defined as *S. aureus* bacteraemia with a central line or implanted device which was not removed, or a focus which was hard for antibiotics to penetrate, such as a deep-seated abscess, or metastatic sites of infection. For three patients only, there was a protected focus (abscess or endocarditis), which could have arisen after the infection, or may have been present in a cryptic state before diagnosis. These cases were recorded as having an adverse outcome and complicated disease.

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### Statistical analysis

Statistical analysis was performed to determine effects of appropriate antibiotic therapy duration on outcomes and recurrent infection. Patients who died while still receiving antibiotics were excluded from this analysis, as their treatment course was curtailed by death. Patients were divided into three groups according to antibiotic duration: <14 days, 14–27 days and >27 days. As several variables showed a skewed distribution, comparisons between groups were made using Kruskall–Wallis test for continuous variables and chi-square or Fisher's exact tests for categorical variables. Logistic regression was performed with adverse outcome as the dependent variable, and independent variables of birth weight, gender, meticillin-susceptibility, maximum CRP, antibiotic duration, and presence of complicated disease. All tests were performed using IBM SPSS Statistics v21.

## Results

A total of 90 infants with *S. aureus* bacteraemia were identified, of which six (7%) were MRSA. There was a preponderance of low gestation and birth weight (Table I), with median gestation of 27 weeks and median birth weight of 846 g. Although median postnatal age was 16 days, peak incidence was in the second week of life (Figure 1).

An underlying diagnosis classically associated with *S. aureus* infection was reported in 10 cases (11%); these were cellulitis or abscess (8), bone or joint infection (1) and line infection (1). In nine cases (10%) there was pneumonia, which may be associated with *S. aureus*. Other diagnoses not normally associated with *S. aureus* included necrotizing enterocolitis and abdominal surgery (9), and congenital abnormality (5). Complicated *S. aureus* infection was found in 17 (19%).

Adverse outcomes were found in 40 cases (44%), which included recurrent or breakthrough *S. aureus* infection (4), death (7), osteomyelitis (2), limb shortening (1), meningitis (4), bacterial endocarditis (1), pneumatocoeles (1), surgical drainage of abscesses (2), necrotizing enterocolitis after the initial illness (6), and increased duration of oxygen requirement (16). Some had more than one adverse outcome.

**Table I**
Characteristics of the whole cohort of 90 infants with *Staphylococcus aureus* bacteraemia

| Characteristics | Values |
|---|---|
| Demographics | |
| Gestational age at birth (weeks)[a] | 27 (23–41) |
| Birth weight (g)[a] | 846 (434–3840) |
| Male gender | 49 (54%) |
| Inborn | 66 (73%) |
| Characteristics at time of positive culture | |
| Postnatal age (days)[a] | 16 (0–116) |
| Corrected GA at episode (weeks)[a] | 31 (23–53) |
| Clinical sepsis | 88 (98%) |
| Classical clinical *S. aureus* disease | 10 (11%) |
| TPN within 48 h of culture | 54 (60%) |
| Enteral feeds during culture | |
| Full | 30 (33%) |
| Partial | 49 (54%) |
| None | 10 (10%) |
| Central line when *S. aureus* isolated | 52 (58%) |
| MSSA | 84 (93%) |
| MRSA | 6 (7%) |
| Treatment | |
| Total duration appropriate antibiotics (days)[a] | 19 (0–54) |
| Duration of antibiotics | |
| 0–13 days | 16 (18%) |
| 14–27 days | 52 (58%) |
| ≥28 days | 21 (23%) |
| Vancomycin used | 41 (46%) |
| Central line removed during infection | 40 (44%) |
| Complicated *S. aureus* infection (plastic device remaining *in situ* or difficult-to-penetrate site) | 17 (19%) |
| Antibiotics curtailed by death or discharge | 9 (10%) |
| Outcomes | |
| Any adverse outcome | 40 (44%) |
| Death | 7 (8%) |
| Recurrent *S. aureus* infection | 4 (4%) |
| Recurrent *S. aureus* bacteraemia | |
| Breakthrough during primary antibiotic course | 1 |
| After completing antibiotics | 0 |

GA, gestational age; TPN, total parenteral nutrition; MSSA, meticillin-susceptible *S. aureus*; MRSA, meticillin-resistant *S. aureus*.
[a] Median (range).

### Recurrent infection

There were no cases of recurrent *S. aureus* bacteraemia after completing the primary antibiotic course. Two infants had non-bacteraemic recurrent *S. aureus* infection; one with a respiratory infection requiring reintubation in the neonatal unit, the other with *S. aureus* otitis media during readmission to paediatric wards.

Two patients had breakthrough *S. aureus* infection during their primary antibiotic course. One had breakthrough *S. aureus* bacteraemia six days after starting antibiotics; this infant was colonized with *S. aureus* at birth and had *S. aureus* cultured from maternal expressed milk, so may have been reinfected. Another preterm infant with osteomyelitis had *S. aureus* cultured locally from abscesses eight days after starting treatment. There were no differences in clinical characteristics or antibiotic duration between those with recurrent or breakthrough disease and the remaining cohort.

### Antibiotic duration and adverse outcomes

Appropriate antibiotics were given for a median of 19 days (range: 0–54). Flucloxacillin without vancomycin was used in 51%, vancomycin without flucloxacillin in 19%, with both flucloxacillin and vancomycin used in 27%. Aminoglycosides were used in 41%. Antibiotics were given for a median duration of 21 days in complicated disease compared with 19 days in uncomplicated cases.

In nine patients the antibiotic course was curtailed by death or discharge to another unit; two had incomplete data on curtailment. Of 16 patients receiving antibiotics for less than two weeks, seven had their course curtailed, leaving 79 in whom the association between antibiotic duration and outcomes could be determined. Examining antibiotic duration by

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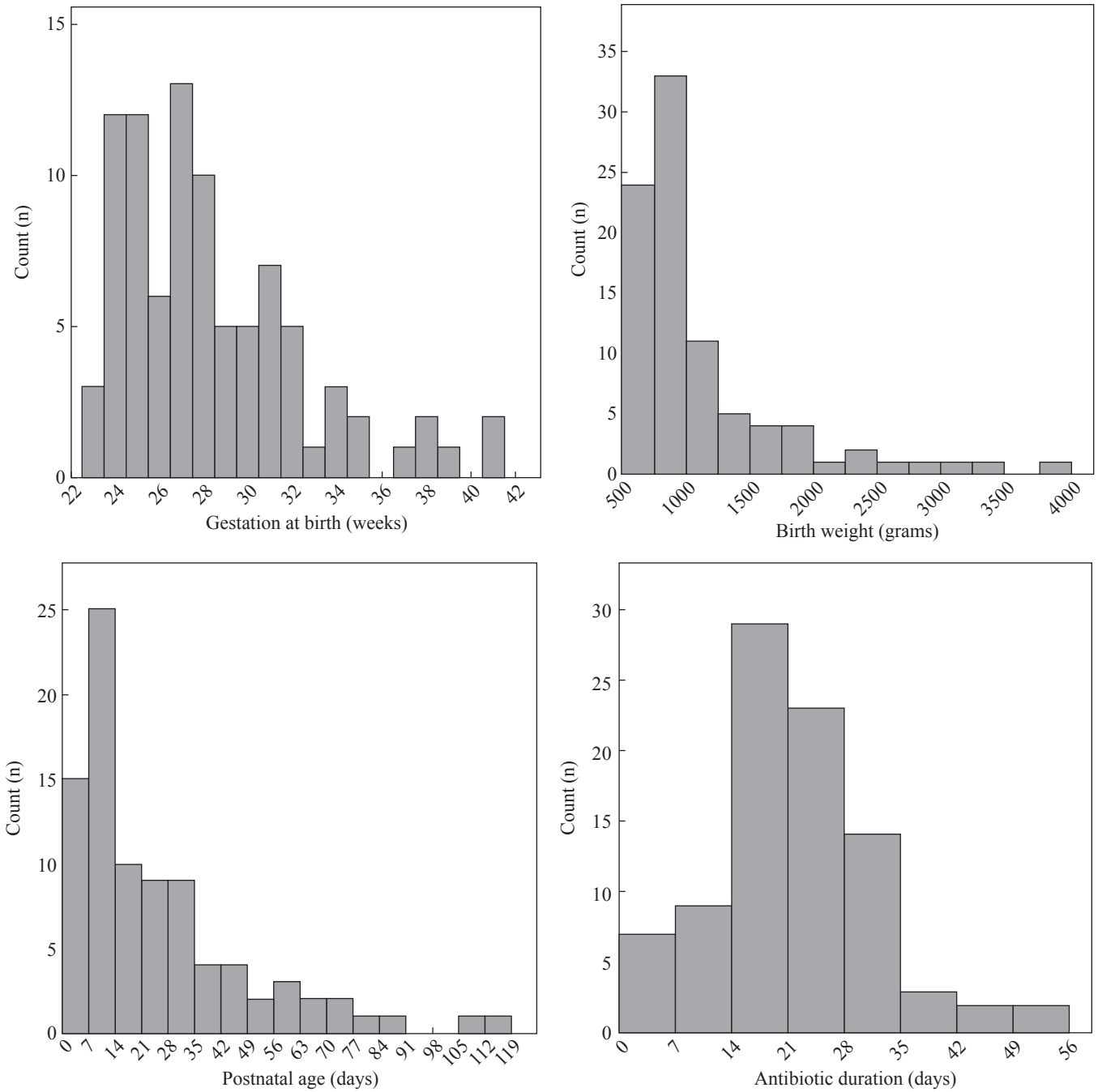


**Figure 1.** Gestation, birth weight, postnatal age distribution, and duration of antibiotic therapy. There was a preponderance of low gestation and low birth weight infants with peak incidence in the second week of life.

group (<14 days, 14–27 days, >27 days) there were no statistically significant differences in any parameter, but all those treated for <14 days had uncomplicated disease (Table II).

On univariate analysis, patients with adverse outcomes were more likely to be of low gestation or birth weight and to have complicated disease, and had a higher CRP (Table III). In stepwise logistic regression analysis, retained variables showed that the odds for adverse outcome increased with maximum CRP (odds ratio: 1.009; 95% confidence interval: 1.000–1.018), were inversely related to birth weight (0.998; 0.996–0.999), and increased in the presence of complicated disease (16.97; 2.55–113.0).

### *Deaths in S. aureus bacteraemia*

In three of the seven infants who died, staphylococcal sepsis was a stated cause of death. However, three others died soon after their positive *S. aureus* blood culture, suggesting that *S. aureus* infection contributed to death. Most who died were <26 weeks of gestation or <1000 g birth weight. The only term infant who died had harlequin ichthyosis, with impaired cutaneous barrier function and a central line left in place. Both infants with MRSA who died received vancomycin. Median time from positive *S. aureus* blood culture to death was two days (range: 1–19).

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**Table II**
Characteristics and outcomes for the 79 patients whose antibiotic course was not curtailed by death or discharge

| Characteristics and outcomes | Duration of appropriate antibiotics | | | *P*-value |
|---|---|---|---|---|
| | 0–13 days | 14–27 days | ≥28 days | |
| | (*N* = 9) | (*N* = 51) | (*N* = 19) | |
| Patient demographics | | | | |
| Gestation (weeks)[a] | 28 (23–41) | 28 (23–41) | 27 (24–38) | 0.364 |
| Birth weight (g)[a] | 990 (500–3840) | 890 (590–3075) | 800 (530–2990) | 0.894 |
| Infection episode | | | | |
| Corrected GA at episode (weeks)[a] | 34 (29–44) | 31 (23–41) | 32 (24–53) | 0.156 |
| Clinical sepsis | 8 | 51 | 19 | 0.11 |
| Maximum CRP within 72 h[a] | 24 (0–148) | 47 (0–280) | 57 (0–340) | 0.310 |
| Organism, no. (%) | | | | |
| MSSA | 9 | 50 | 16 | 0.103 |
| MRSA | 0 | 1 | 3 | |
| Central line when *S. aureus* isolated | 4 | 29 | 11 | 0.84 |
| Central line not removed | 0 | 4 | 3 | 0.38 |
| Complicated (plastic device remaining *in situ* or difficult-to-treat site) | 0 | 9 | 5 | 0.24 |
| Outcomes | | | | |
| Any adverse outcome | 2 | 21 | 9 | 0.46 |
| Recurrent *S. aureus* infection | 0 | 3 | 1 | 1.00 |
| Death | 0 | 0 | 0 | – |

GA, gestational age; CRP, C-reactive protein; MSSA, meticillin-susceptible *S. aureus*; MRSA, meticillin-resistant *S. aureus*.
[a] Median (range).

## Discussion

This study has described the clinical features of *Staphylococcus aureus* bacteraemia in a large cohort of infants admitted to neonatal units. The patients were predominantly preterm and many had associated conditions. There were high rates of complications and mortality, attributable to both *S. aureus* disease and underlying conditions. A predominance of disease at lower birth weight has been previously reported.[2] Although 11% had a focus typical of *S. aureus* disease, the majority had bacteraemia without any focus.

Patients with adverse outcomes had lower gestation and birth weight, higher CRP and were more likely to have complicated disease, including retained central venous lines. This is consistent with research suggesting that central catheter retention is associated with adverse outcomes in neonates

**Table III**
Characteristics of patients with and without adverse outcomes

| Characteristics | No adverse outcome (*N* = 50) | Adverse outcome present (*N* = 40) | *P*-value |
|---|---|---|---|
| Demographics | | | |
| Gestation (weeks)[a] | 28.5 (23–41) | 25.5 (23–37) | 0.001 |
| Birth weight (g)[a] | 980 (500–3840) | 760 (434–2990) | 0.006 |
| Male sex | 26 (52%) | 23 (58%) | 0.60 |
| Episode | | | |
| Postnatal age (days)[a] | 13 (1–110) | 22.5 (0–116) | 0.23 |
| Corrected GA at episode (weeks)[a] | 32.0 (26–53) | 30.5 (23–44) | 0.051 |
| Maximum CRP within 72 h[a] | 32 (0–193) | 63 (0–340) | 0.023 |
| Central line when *S. aureus* isolated | 31 (62%) | 21 (53%) | 0.44 |
| Organism: MRSA | 1 (2%) | 5 (13%) | 0.09 |
| Treatment | | | |
| Total duration appropriate antibiotics (days)[a] | 20 (0–50) | 17 (0–54) | 0.81 |
| Vancomycin used | 19 (38%) | 22 (55%) | 0.084 |
| Central line removed during infection | 28 (56%) | 12 (30%) | 0.026 |
| Complicated (plastic device remaining *in situ* or difficult-to-treat site) | 3 (6%) | 14 (35%) | 0.001 |

GA, gestational age; CRP, C-reactive protein; MRSA, meticillin-resistant *S. aureus*.
Analysis performed on all 90 patients.
[a] Median (range).

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with *S. aureus* or Gram-negative bacteraemia.[15] In logistic regression, low birth weight, high CRP, and complicated disease carried an increased risk for adverse outcomes. These findings are limited by our study's retrospective design. Although patients with persisting disease markers were investigated for metastatic foci, this was decided individually by discussion between clinicians and microbiologists, with no fixed protocols for repeat blood cultures, further investigation, or antibiotic duration.

The guidelines for adults and children define uncomplicated disease by exclusion of endocarditis, with no metastatic sites or implanted prosthesis, and rapid disease control.[11] This definition cannot be directly applied in neonates, in whom it is hard to exclude bacterial endocarditis. To retain the concept of difficult source control, complicated disease was defined as the presence of a central line or other foreign material which was not removed, a focus which was hard for antibiotics to penetrate, or metastatic sites of infection. Using this definition, complicated disease was not a risk factor for adverse outcome or recurrence, but all complicated cases had planned antibiotic courses of over two weeks. The favourable outcomes with less than two weeks of therapy may have been achieved because none had complicated disease.

There was no association between antibiotic duration and complications or recurrence. Only one infant was identified with bacterial endocarditis. In adults, Asgeirsson *et al*. found that in complicated *S. aureus* bacteraemia, duration of intravenous antibiotic therapy was 16 days in those experiencing a relapse and 30 days in those who did not.[6] However, Walker *et al*. did not find an association between curtailed antibiotic therapy and recurrence.[5] They found that recurrence was associated with keeping a central line in place and with glycopeptide treatment of meticillin-susceptible *S. aureus*.

No cases of recurrent bacteraemia were found after finishing antibiotics, and only one case of breakthrough bacteraemia occurred during treatment. Preterm infants in this study stayed in hospital for many weeks before discharge home, allowing detection of early recurrence. Although some patients were transferred in from other areas, 73% were inborn and would have been readmitted to the same hospital with recurrent disease. Although late recurrence rates could have been slightly underestimated, they were certainly very low. As endocarditis is a major factor in adult recurrent disease, this suggests that the newborn may be relatively well protected against *S. aureus* endocarditis. *In vitro*, shear stress reduces adherence of *S. aureus* to endothelial cells.[16] Children and newborn infants have a higher cardiac output per unit body weight than adults, with the highest values in extremely preterm infants.[17–19] This could produce greater shear forces at the endothelial interface and protect the normally vulnerable neonate against *S. aureus* endocarditis.

The proportion of our patients with MRSA was only 7%, comparable with 8% found in another UK series, but lower than the 33% reported in a US series.[1,2] A non-significant trend for more adverse outcomes with MRSA was found. Enhanced surveillance of MRSA bacteraemia in children reported a low proportion (1.9%) with endocarditis.[20] However, in a series of MRSA bacteraemia cases, Chuang *et al*. reported recurrent bacteraemia in seven out of 82 (8.5%) infants; all were treated with ≤14 days of vancomycin and four had catheter-related infection.[21]

Most infants who died were extremely preterm, suggesting that *S. aureus* bacteraemia may be particularly hazardous in this group. The approach to source control was adequate in those who died; only one infant with severe vascular access difficulties had a central line left in place. The median time from positive *S. aureus* blood culture to death was two days.

Our study is the largest series of neonatal *S. aureus* bacteraemia relating clinical outcomes to duration of antibiotic treatment. No link was found between duration of antibiotic therapy and adverse outcomes, but clinicians used longer courses of antibiotics for more complicated cases. Rates of endocarditis and recurrent bacteraemia were low. Given the problem of early mortality, the clinical priority is to implement strategies to prevent colonization and reduce early mortality. Removal of protected sources such as central lines may also be important to prevent recurrence. We suggest that in neonates with *S. aureus* bacteraemia it is reasonable to apply the adult recommendations for antibiotic therapy of 14 days in uncomplicated cases, and longer for cases with inadequate source control.

**Conflict of interest statement**
None declared.

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