Irish Journal of Medical Science (1971 -) (2019) 188:1297–1301
https://doi.org/10.1007/s11845-019-01992-y

ORIGINAL ARTICLE

A retrospective study (2001–2017) of acute and chronic morbidity and mortality associated with *Staphylococcus aureus* bacteraemia in a tertiary neonatal intensive care unit

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Received: 10 October 2018 / Accepted: 16 February 2019 / Published online: 25 February 2019

Abstract

Background *Staphylococcus aureus* bacteraemia (SAB) in NICU patients can cause significant morbidity and mortality.
Aims To review early and late neonatal SAB with regard to risk factors, treatment, acute complications and long-term outcomes.
Methods A retrospective study of laboratory confirmed SAB over a 16-year period (November 2001–January 2017) in a tertiary neonatal unit in Ireland.
Findings A total of 74 neonates (MSSA $n = 72$, MRSA $n = 2$) were identified; 8.1% ($n = 6$) early sepsis, 91.8% ($n = 68$) late sepsis. Low birth weight neonates (born weighing less than 2500 g) 80% ($n = 59$). Median age to bacteraemia 11 days post-delivery (range = 0–100 days); median onset early sepsis 1.5 days versus late sepsis 12 days. Complications of SAB; cellulitis $n = 17$, pneumonia $n = 12$, necrotising enterocolitis $n = 7$, thromobophlebitis $n = 5$, skin abscess formation $n = 4$, osteomyelitis $n = 3$, endocarditis $n = 1$. Late SAB mortality 6.4% ($n = 3$).
Conclusions Preterm and low birth weight infants were at highest risk of SAB. Only a small proportion of affected children had long-term clinical sequelae on follow-up. The high rate of recurrence and breakthrough bacteraemia suggests that early implementation of a targeted anti-staphylococcal antimicrobial regimen may be of particular benefit.

Keywords Neonatal intensive care unit · Outcomes · *Staphylococcus aureus* bloodstream infection

Introduction

Staphylococcus aureus is the second commonest pathogen found in neonatal bacteraemia in the UK, causing significant neonatal morbidity and mortality (20–35%). It is frequently implicated in device-related sepsis in neonatal intensive care units (NICUs), despite advances in NICU care including the implementation of care bundles, improved hand hygiene compliance rates and better environmental hygiene standards [1–4]. Risk factors for *S. aureus* bacteraemia (SAB) in NICUs include prematurity [1], nasal *S. aureus* colonisation [2] and the presence of either intravascular catheters (peripheral and central) or implanted devices [3].

Localised *S. aureus* neonatal infections can occur with or without bacteraemia. Direct tissue invasion such as cellulitis may not be associated with positive blood cultures, while severe infections such as staphylococcal scalded skin syndrome, pneumonia, endocarditis, brain abscess formation, pyomyositis, osteomyelitis and septic arthritis typically occur with overt clinical septicaemia [4–6]. The production of toxins by *S. aureus* may result in toxic shock syndrome [7].

The aims of this study were (1) to establish the mortality and morbidity attributable to SAB in neonates, (2) to identify risk factors for SAB, (3) to look at the variance in clinical practice in regard to the management of SAB in terms of choice and duration of initial antimicrobial regimen of antimicrobials and (4) to investigate any long-term adverse clinical

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sequelae of SAB identified in infants who attended paediatric outpatient clinics at our hospital.

Materials and methods

Setting

The Rotunda Hospital is a university-affiliated national referral centre for maternity and neonatal patients. It has approximately 8500 deliveries per annum and 1300 admissions per annum to the 39-bedded tertiary NICU.

Ethics

Ethical approval was received from the local ethics committee to conduct this study.

Study design

A retrospective, single centre study was performed using the laboratory management system (APEX) to identify cases. A manual paper and electronic chart review for each case was also performed.

Study definitions

Bacteraemia was defined as the isolation of *S. aureus* from a blood culture, taken from a peripheral vein or via an indwelling central line. Clinical sepsis was defined as bacteraemia requiring treatment with antibiotics associated with clinical signs in the neonate and/or raised haematological and/or biochemical results such as C-reactive protein (CRP). Recurrence was defined as any clinical illness with isolation of *S. aureus* after stopping appropriate antimicrobial therapy recorded in the hospital or laboratory record during the same inpatient admission, including both bacteraemia and localised disease. Breakthrough disease was defined as a positive *S. aureus* blood culture during the primary antimicrobial course in the absence of the detection of an antimicrobial resistance mechanism. Early sepsis was defined as within the first 72 h of life in cases. Late sepsis was defined as sepsis occurring beyond these time points. Low birth weight infants (LBW) were those with a birthweight less than 2500 g, and very low birth weight (VLBW) infants were those weighing < 1500 g at birth. Uncomplicated sepsis was defined as cases where the following criteria were met: (1) catheter-associated infection with removal of catheter, (2) negative result of follow-up blood culture, (3) resolution of clinical features/instability within 72 h and (4) no symptoms suggestive of metastatic infection. Line sepsis was defined as bloodstream infection in the presence of a venous catheter (peripheral or central) or within 48 h of removal of the catheter and which cannot be attributed to an infection unrelated to the catheter.

Study population (inclusion and exclusion criteria)

All infants admitted to the NICU of the Rotunda Hospital were considered eligible for inclusion in this study if they had laboratory confirmed SAB.

Data collation and statistics

Laboratory microbiology databases were used to identify all cases of SAB in admissions to the NICU over a 16-year period (November 2001 to January 2017). Clinical details relevant to the study aims were extracted via a manual search of medical records for all admissions until July 2017. Laboratory values (WCC, neutrophils, platelets, CRP) were extracted from electronic records. Follow-up occurred in accordance with local neonatal practice with extremely preterm and low birth weight infants followed to at least 24 months corrected gestational age and infants who were late preterm and normal weight followed up at the discretion of treating consultant in the paediatrics outpatient department and with a focus on achievement of appropriate developmental milestones, for corrected age in months and relevant comorbidities. Comparisons were made using the Mann–Whitney *U* statistical test.

Follow-up

Premature infants were followed up as per local clinical protocol. Infants transferred from other hospitals either ante- or postnatally were followed up by their referring hospital.

Results

Epidemiological

A total of 74 neonates were identified for inclusion in the study of whom 8.1% ($n = 6$) met the definition criteria for early sepsis and 91.89% ($n = 68$) met definition criteria for late sepsis; 51% ($n = 38$) male. Low birth weight babies (born weighing less than 2500 g) accounted for with 79.72% ($n = 59$). A total of 59% ($n = 44$) were described as very low birth weight (< 1500 g) and 35.13% ($n = 26$) as extremely low birth weight (< 1000 g). The birth weight of infants affected by early sepsis was higher than the late sepsis group, median 2690 g (range 800–4470 g) versus 1250 g (range 470–4300 g; $p = 0.048$).

The majority of infants in this study were preterm (77.1%, $n = 57$), with very preterm (28–32 weeks) and extremely preterm (< 28 weeks) accounting for 20.3% ($n = 15$) and 36.5% ($n = 27$) respectively. The corrected gestational age of babies

with early onset sepsis (median 38.0 weeks (range = 26.28–40) was older than those with late onset SAB (median 32.49 weeks (range = 25–42.14) although this did not reach statistical significance ($p = 0.17$), and 79.41% of infants with late SAB were premature.

The median age to bacteraemia was 11 days post-delivery (range = 0–100), with the median age for early and late sepsis reflecting the differences in definition of these two entities, with early sepsis having a median onset of 1.5 days (range = 0–3) and late sepsis occurring at 12 days (range 4–100). One neonate in the early sepsis group was born to a mother with ongoing SAB sepsis. Identifiable maternal risk factors were only found in 5.6% ($n = 3$) of the late onset SAB group. Of the neonates who went on to develop late sepsis, a relatively smaller cohort of 5.6% ($n = 3$) had identifiable maternal risk factors; $n = 1$ prolonged premature rupture of membranes (PPROM), and two neonates whose mothers were intravenous drug users (IVDUs).

Antimicrobial susceptibility patterns

A total of 97.3% ($n = 72$) of SAB isolates were methicillin sensitive *S. aureus* (MSSA). The remaining two cases identified as methicillin sensitive *S. aureus* (MRSA) but occurred 11 years apart and were both late onset occurring at 33 and 44 days of life.

Antimicrobial therapy received

There was no NICU policy differentiation between therapy for early or late SAB during the study timeframe. A total of 86.5% ($n = 64$) of neonates were treated with flucloxacillin and gentamicin as first line antimicrobial therapy as per NICU policy for late onset sepsis (LOS); 31.2% ($n = 20$) received high dose (> /=50 mg/kg) flucloxacillin and the remainder received standard dose flucloxacillin (< 50 mg/kg). There was variance with regard to treatment regimens adopted for SAB but flucloxacillin and cefotaxime were the two most common regimes, accounting for 5.4% ($n = 4$) of all prescriptions. This may reflect the renal status of infants at the time of diagnosis. 16.1% ($n = 12$) received an initial antimicrobial regimen other than flucloxacillin with gentamicin. Of the babies who did not receive standard LOS antimicrobial treatment, 94.1% ($n = 16$) were switched to flucloxacillin and gentamicin when blood cultures returned as SAB. 31% ($n = 23$) of those studied received vancomycin during their clinical course with a median duration of vancomycin therapy of 7 days (range = 1–22 days).

Most infants (68.9%, $n = 51$) had been treated with antimicrobials before their episode of SAB, with 78.4% ($n = 40$) getting antibiotic prophylaxis during the first 36 h after birth. 5.4% ($n = 4$) received antibiotics due to a confirmed previous (non *S. aureus*) infection. The average duration of antibiotic therapy was 12 days (range 0–44 days). Flucloxacillin was administered for a median of 10 days (range 1–42) whereas gentamicin was prescribed for a median of 7 days (range 1–20) (Fig. 1).

Breakthrough or recurrent SAB

Breakthrough or recurrent SAB occurred in 27% ($n = 20$) of infants studied, 60% ($n = 12$) of whom were on routine (< 50 mg/kg/dose) flucloxacillin and gentamicin, and 30% ($n = 6$) of whom were on high dose (> 50 mg/kg/dose) flucloxacillin and gentamicin. One infant had an MRSA bacteraemia.

Neonatal clinical course

The most common clinical indication for the initial blood cultures was an increase in either oxygen requirements or work of breathing (32.4%, $n = 24$). Pyrexia was found in 29.7% ($n = 22$) and specific suspicion of a staphylococcal illnesses (e.g. cellulitis, abscesses or scalded skin syndrome) was present in 25.7% ($n = 19$). Other common reasons for taking blood cultures were instability (bradycardic episodes in 17.6%, $n = 13$), babies described as being 'quiet' or 'pale' 9.5% ($n = 7$) and jaundice 5.4% ($n = 4$).

Complicated and uncomplicated SAB

88.7% ($n = 47$) of neonates with late onset SAB had a complicated course. Babies with an uncomplicated course were more likely to be male (57%, $n = 27$) versus 42.5% ($n = 20$) females), had a smaller birth weight; median of 1225.6± 738 g compared with 1636± 1020 g. Most infants with a complicated sepsis were premature (< 37 weeks, 95.7% ($n = 45$)) had a peripheral line in situ and 48.9% ($n = 23$) had a central line at the time of SAB. 53.1% ($n = 25$) had received total parenteral nutrition (TPN) within 48 h of their culture. Additionally, those with complicated sepsis in the late onset cohort (28.14; range = 20.71–40.71 weeks gestation) were more preterm than those with an uncomplicated course (median = 36.78; range = 30–41 weeks; $p = .00001$).

Of babies with complicated sepsis, 68.9% ($n = 51$) had a respiratory complication. An increased oxygen requirement was seen in 70.5% ($n = 36$), 23.5% ($n = 12$) had pneumonia and 5.9% ($n = 3$) had a pneumatocele on chest x-ray film. Soft tissue or musculoskeletal complications were seen in 33.8% ($n = 25$), of which 68% ($n = 17$) were cellulitis or abscess formation and 23.5% ($n = 4$) of these required drainage for source control. Osteomyelitis was found in 12% ($n = 3$) and one child had associated limb shortening resulting in a chronic limp. Four infants (16%) had septic arthritis which involved either their hips ($n = 4$) or their elbows ($n = 1$) with half of these ($n = 2$, including the infant with limp above) having subsequent

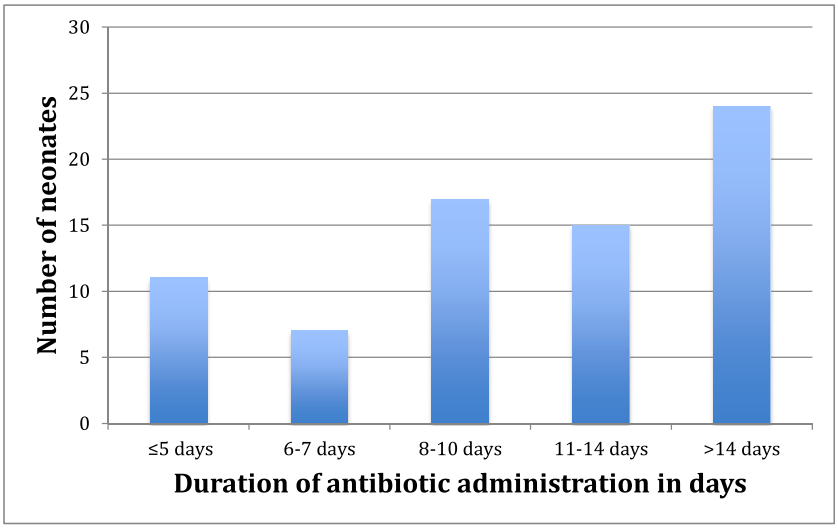

Fig. 1 Histogram illustrating duration of antibiotic treatment in neonates

subluxation of their hip requiring Pavlik Harness. The fourth infant with septic arthritis had a normal outcome. Necrotising enterocolitis (NEC) was suspected in 18 neonates at the onset of SAB and confirmed in seven of these infants (39%). Three infants with confirmed NEC required subsequent surgical intervention. Line sepsis accounted for 52.7% ($n = 39$) of SAB. One infant had proven endocarditis, one had meningitis and five (6.7%) had thrombus with thrombophlebitis.

Mortality secondary to SAB

The mortality rate in infants with late SAB was 6.4% ($n = 3$) in this cohort. Comorbidities were present in all three: two infants were extremely premature (born at 23 and 25 weeks respectively) and the third had endocarditis complicating a coarctation of the aorta.

Follow-up

Two-thirds of infants were followed up in the Rotunda outpatient department, comprising 67.4 infant years of follow-up. Of these, only two infants had problems attributable to SAB, with one child having both subluxation of the hip and limb shortening and another requiring a harness for subluxation of the hips.

Discussion

This study describes the clinical course, therapeutic strategies and associated outcomes for neonates with SAB. A unique aspect of this retrospective analysis is the volume of follow-up data collected which demonstrated that in the large cohort of patients followed up after discharge from NICU, there was a low rate of complications directly connected with their previous SAB. This is encouraging for parents and clinicians involved in the care of these infants. A caveat to this is that a minority of patients were not followed up in our own hospital but instead either attended their referring centre or were referred onwards to other specialist centres for other clinical problems, including complications due to prematurity and other coexisting conditions. One was referred to a paediatric metabolic medicine clinic and two required urology follow-up for structural urinary tract abnormalities. Additionally, as data was collected manually from paper charts, it is possible aspects of each infant's clinical course were missed either from documentation or on review.

Our data confirms that preterm infants are at high risk of SAB with 77.1% of babies in this study born at less than 37 weeks gestation. Similarly, ~ 80% of our cohort were low birth weight babies (< 2500 g) and median age to onset of bacteraemia was 11 days, all of which compares with data collected elsewhere, strengthening the evidence about the subsets of babies affected by SAB [3, 8].

The mortality rate of 6.4% in this SAB cohort is comparable with studies performed in both the US and the UK which have shown overall mortality of 7–16% [9, 10]. An interesting finding in our cohort is the relatively high rate of pyrexias as a clinical sign of infection with 29.7% of patients screened secondary to pyrexia. This contrasts with other studies, which have reported fever in only 16–20% of patients with neonatal sepsis [11, 12]. Whether or not this is specific to the pathophysiology of SAB in this population is difficult to say, given the paucity of papers reporting on specific clinical indications for blood culture in neonates.

The type and incidence of complications due to SAB were similar to other reports, with skin or soft tissue infections and pneumonia being common. This is not surprising given the known association between *S. aureus* and skin infections, and the number of these babies receiving mechanical ventilation,

which is itself a risk factor for respiratory tract infection with *S. aureus* [13, 14] . Only one case of endocarditis was reported in our study.

The majority of patients received flucloxacillin and gentamicin as either initial therapy or as modified therapy once the blood culture results was available. Despite the available range of antimicrobial regimens, all neonates received anti-staphylococcal cover as part of their empirical antibiotic therapy on the day the positive blood culture was obtained [15]. However, 27% of neonates had recurrence or breakthrough infection, suggesting early implementation of optimum antimicrobial therapy is important in this cohort.

Conclusions

Overall, neonates in our cohort had a good long-term prognosis, despite a high morbidity and mortality in the acute illness, with only a small proportion of affected children suffering long-term clinical sequelae from their infection. Preterm and low birth weight infants were disproportionately represented in the study suggesting these babies are at high risk of SAB. Early sepsis was rare in this group although the only case of clear vertical transmission was found in this small subset. While adequate empiric antibiotic cover was universally implemented, a high rate of recurrence and breakthrough suggests early optimization and rationalisation of antibiotic regimens is important in care in this patient group.

Compliance with ethical standards

Ethical approval was received from the local ethics committee to conduct this study.

Conflict of interest The authors declare that they have no conflict of interest.

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