Five-year prospective surveillance of nosocomial bloodstream infections in an Estonian paediatric intensive care unit

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SUMMARY

Background: Few studies provide rates of nosocomial bloodstream infections (BSIs) in mixed neonatal and paediatric intensive care units (PICUs).

Aim: To determine the rate, pathogens and outcome of BSIs in an Estonian PICU.

Methods: Data were collected prospectively from 1st January 2004 to 31st December 2008 in the PICU of Tartu University Hospital. The definition criteria of the US Centers for Disease Control and Prevention were applied for the diagnosis of laboratory-confirmed BSI.

Findings: A total of 126 episodes of BSI were identified in 89 patients (74 neonates, eight infants, seven patients aged >1 year). Among neonates 42 (57%) had birth weight <1000 g. The overall incidence of BSI was 9.2 per 100 admissions, incidence density 12.8 per 1000 patient-days. Primary BSI was diagnosed in 92 episodes. Central line (CL)-associated BSI incidence density for neonates was 8.6 per 1000 CL-days with the highest incidence (27.4) among neonates with extremely low birth weight. The most common pathogens were coagulase-negative staphylococci (43%) and Serratia marcescens (14%). Resistance to meticillin was detected in four out of seven S. aureus isolates (all were part of an outbreak) and 23% of Enterobacteriaceae were extended spectrum beta-lactamase (ESBL)-producing strains. Overall case-fatality rate was 10%.

Conclusion: We observed higher rates of BSIs in our mixed PICU than reported previously. High levels of antimicrobial resistance were detected. Future research should focus on the effects of infection control measures to prevent outbreaks and to decrease incidence of CL-associated BSI.

Introduction

Advances in neonatal intensive care have improved the survival of preterm infants. These patients are at high risk of healthcare-associated infections (HCAIs) due to their immature immune system and the high prevalence of invasive devices and procedures. Nosocomial bloodstream infection (BSI) rates
range from 10% for all neonates to 50% in extremely low birth weight (ELBW; birth weight <1000 g) infants and are associated with high mortality, increased costs, and adverse neuro-developmental outcomes.4

Patients in paediatric intensive care units (PICU) represent a diverse range of underlying diseases and are at risk of BSI.1,5 The type of PICU (such as surgical versus medical; referral centre versus general hospital) as well as the patients' clinical characteristics may account for differences observed in the incidence of BSI.

In our mixed PICU, the patient population ranges from ELBW neonates to adolescents comprising a wide variety of conditions including congenital malformations requiring surgical repair; paediatric emergencies including multiple trauma, near-drowning or poisonings; infectious diseases and other neonatal conditions.

We have previously reported the results of a 2-year study of BSIs in three of the largest hospitals of Estonia.6 The data from PICU were not analysed separately in this study. Few studies provide BSI rates in mixed PICU and even fewer data are available from Eastern Europe.7 The aim of the present study was to determine the rate, pathogen spectrum and outcome of BSIs in a mixed PICU in Estonia.

**Methods**

**Setting**

Tartu University Hospital is a 960-bed tertiary care teaching hospital with ~43,000 admissions annually. It serves a population of 600,000 and includes 5000 births per year (2004 national data, pub.stat.ee). The PICU (level III) has nine beds and treats ~250 admissions annually of which 50–60% are neonates. Patients are admitted from home, from other units within the hospital such as haematology, cardiac surgery and the maternity unit, and from district hospitals. The PICU consists of five rooms and there are three single rooms.

The Department of Infection Control (IC) was established in 2003. IC personnel visit PICU at least once a week. Guidelines for the prevention of central line (CL)-related infections have been implemented since 2007.

When BSI is suspected at least one blood culture is obtained, preferably before empirical antibiotic treatment. A total of 1553 blood culture sets were collected (268 per 1000 patient-days) and in 89% of cases only one sample was taken (2004–2006 data). In cases of suspected early onset neonatal sepsis, empirical gentamicin with ampicillin is used for very low birth weight infants (VLBW; birth weight <1500 g) or with penicillin G in other neonates. In other infants and children, cefotaxime with gentamicin is the preferred empirical therapy for sepsis. Fluconazole prophylaxis is administered to ELBW neonates. Risk factor-based intrapartum prophylaxis with penicillin G is used for the prevention of perinatal group B streptococcal disease.

**Patients and data collection**

Surveillance for BSI was conducted from 1st January 2004 to 31st December 2008. Term and preterm babies (<33 gestational weeks) were considered neonates up to 28 and 90 days of age, respectively. Clinical and microbiological data were collected prospectively by IC personnel using a standardized case-report form as previously described.6 Each episode was classified as BSI based on the guidelines of the US Centers for Disease Control and Prevention (CDC).8 Only laboratory-confirmed BSIs occurring more than 48 h after PICU admission were included. To diagnose BSI with blood culture isolates comprising skin commensals, clinical signs of infection were required along with: (i) two or more separate blood cultures of phenotypically similar organism or (ii) one blood culture in patients with an indwelling CL and appropriate antimicrobial therapy at least for 5 days or resolution of symptoms after the device had been removed. Repeatedly positive samples with a phenotypically similar organism were considered the same episode if the period between the samples did not exceed 7 days. Polymicrobial BSI was defined as the isolation of different species from one or more blood cultures within 48 h.

BSIs were classified as primary (CL-associated or unknown origin) or secondary (infection in a distant body site). The use of CLs including umbilical catheters was documented daily.

Survival status was recorded one week after the onset of BSI and at hospital discharge.

**Microbiological methods**

Blood was collected into a BACTEC Peds Plus/F bottle and monitored with the BACTEC 9240 blood culture system (Becton Dickinson, Sparks, MD, USA). Bacterial isolates were identified by routine methods and verified by biochemical identification systems: VITEK2 Compact or API tests (bioMérieux, Marcy l’Etoile, France). Antimicrobial susceptibility was determined according to the recommendations of the Clinical and Laboratory Standards Institute.9

**Data analysis**

SPSS software, version 17.0 (SPSS) was used in statistical analyses. BSI incidence (number of BSIs per 100 admissions), BSI incidence density (number of BSIs per 1000 patient-days), CL-associated infection rate (number of CL-associated infections per 1000 CL-days), and CL utilization ratio (number of CL-days per patient-days) were calculated. As blood cultures with coagulase-negative staphylococci (CoNS) may represent either infection or contamination, the BSI incidence and incidence density were also reported with these micro-organisms excluded from the analysis.

**Results**

During the study period 1363 PICU admissions occurred including 745 (55%) neonates. In total 126 BSI episodes were identified in 89 patients (56% male): 74 neonates; eight infants; seven patients aged 1–7 years. The most common underlying diseases in patients with BSI are shown in Table I.

The overall incidence of BSI was 9.2 per 100 admissions and the incidence density 12.8 per 1000 patient-days. Having excluded cases caused by CoNS, the respective rates were 5.1 and 7.1.

Multiple BSI episodes occurred in 26 patients of which 17 patients had two, seven patients had three and two patients
had four episodes. In total 99 (79%) episodes occurred in 74 (83%) neonates; median [interquartile range (IQR)] birthweight was 1000g (740–1400) and the age at the time of BSI diagnosis was 7 days (5.0–11.75). There were 42 (57%) neonates with ELBW.

The median (IQR) age of infants at the onset of BSI was 125.5 days (110.5–163.2).

All patients had at least one risk factor: 70% had CL (median duration 8 days before onset of BSI; IQR: 5–13.25); 48% arterial catheter (7 days; 5–9.5); 57% had two or more intravascular catheters; 44% were mechanically ventilated (8 days; 5–13); 38% received total parenteral nutrition, a urinary catheter was present in 7% and a nasogastric tube in 74% of patients; 33% had 38% received total parenteral nutrition, a urinary catheter was present in 7% and a nasogastric tube in 74% of patients; 33% had a central catheter (7 days; 5–13).

The median (IQR) length of PICU stay was 9 (5–17) days before a BSI episode.

Primary BSI was diagnosed in 92 (73%) episodes, 67 of which were considered CL-associated. The median (IQR) duration of CL prior to CL-associated BSI was 7 (5–13) days. The overall CL-associated BSI incidence density for neonates was 8.6 per 1000 CL-days with the highest incidence among ELBW neonates (Table II). A total of 34 episodes were defined as secondary, most frequently associated with lower respiratory tract (14 cases) or intra-abdominal infections (seven cases).

Nine patients (10%), eight of them neonates, died during the hospital stay. The case-fatality rate within 7 days after the first positive blood culture was 1%. BSIs caused by Candida spp. were not associated with increased mortality in this study.

Pathogens

In total, 136 isolates were recovered from 126 BSI episodes and 8% of BSI episodes were polymicrobial. Gram-positive and Gram-negative micro-organisms accounted for 60% and 35%, respectively. The most common pathogens were CoNS (43%) and Serratia marcescens (14%) (Table III). From July 2005 to December 2009 an outbreak occurred with 210 patients colonized or infected with S. marcescens. Meticillin-resistant Staphylococcus aureus (MRSA) caused an outbreak with 17 affected patients (four BSI) in 2006–2007. There were five isolates of unusual Candida spp.: two Candida albicans, two Candida parapsilosis, one Candida glabrata, three of them in ELBW neonates (7% of all ELBW patients).

Antimicrobial susceptibility of BSI micro-organisms

Resistance to meticillin was detected in four out of seven of S. aureus isolates (all isolated during the outbreak) and in the majority (86%) of CoNS isolates. No resistance to vancomycin was detected among staphylococci and enterococci. Three of the 17 enterococci were ampicillin-resistant Enterococcus faecium. Among 39 Enterobacteriaceae, 88% were resistant to ampicillin, 65% to cefuroxime, 14% to gentamicin, 2% to ciprofloxacin and none to carbapenems. Three isolates of Klebsiella pneumoniae, three S. marcescens and three Enterobacter cloacae (23% of all Enterobacteriaceae isolates) produced extended-spectrum beta-lactamases (ESBL). All Candida spp. except C. glabrata were susceptible to fluconazole and none was resistant to amphotericin B.

Table I

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>No. of admissions</th>
<th>No. of patients with BSI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Neonates 43 100</td>
<td>Children 72 23 (4.1)</td>
</tr>
<tr>
<td>Respiratory system disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular system disease</td>
<td>71 79</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>Trauma and accident</td>
<td>0 81</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>17 121</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Other†</td>
<td>120 165</td>
<td>27 (9.5)</td>
</tr>
<tr>
<td>Total</td>
<td>745 618</td>
<td>89 (6.5)</td>
</tr>
</tbody>
</table>

† Includes haematological diseases, developmental defects requiring surgical repair (e.g. abdominal wall anomalies).

Table II

<table>
<thead>
<tr>
<th>Hospital/ surveillance system</th>
<th>Birth weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1000 g</td>
</tr>
<tr>
<td>Infection rate</td>
<td></td>
</tr>
<tr>
<td>TUH†</td>
<td>27.4</td>
</tr>
<tr>
<td>NNIS14</td>
<td>9.1</td>
</tr>
<tr>
<td>NEO-KISS14</td>
<td>12.6</td>
</tr>
<tr>
<td>Central line utilization ratio</td>
<td></td>
</tr>
<tr>
<td>TUH†</td>
<td>0.42</td>
</tr>
<tr>
<td>NNIS14</td>
<td>0.42</td>
</tr>
<tr>
<td>NEO-KISS†</td>
<td>0.28</td>
</tr>
</tbody>
</table>

†, no observation.
† Includes haematological diseases, developmental defects requiring surgical repair (e.g. abdominal wall anomalies).

Table III

<table>
<thead>
<tr>
<th>Micro-organisms</th>
<th>Neonates</th>
<th>Children &gt;28 days</th>
<th>% of all isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive organisms</td>
<td>68</td>
<td>14</td>
<td>60.3</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>53</td>
<td>5</td>
<td>42.6</td>
</tr>
<tr>
<td>Enterococci</td>
<td>9</td>
<td>8</td>
<td>12.5</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>6</td>
<td>1</td>
<td>5.1</td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td>35</td>
<td>12</td>
<td>34.5</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>13</td>
<td>6</td>
<td>13.9</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>8</td>
<td>2</td>
<td>7.4</td>
</tr>
<tr>
<td>Other Enterobacteriaceae</td>
<td>9</td>
<td>1</td>
<td>7.4</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>4</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>4</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>27</td>
<td>100</td>
</tr>
</tbody>
</table>
Discussion

Most studies have described the epidemiology of BSI either in PICU or neonatal intensive care unit (NICU) and data from mixed units are limited.

In our study the overall rate of BSI was 9.4 per 100 admissions, which is more than twice as high as those reported from surveys in UK and other centres in Europe.11,12 The BSI incidence density (12.8 per 1000 patient-days) was also higher than reported in Finland (3.2 and 2.5 in neonatology and PICU, respectively).13 CL-associated BSI rate and utilization ratio in our study were higher compared with the German Hospital Infection Surveillance System for neonates (NEO-KISS) or US National Nosocomial Infection Surveillance System (NNIS) data.5,14 As our data represent a mixed PICU, the higher incidence of BSI compared with non-neonatal PICU can be explained because neonates, especially ELBW infants, are at the highest risk of BSI.15,16 The results with values exceeding those described in NICU studies require further explanation.

Methodological issues such as whether BSI is secondary, whether more than one episode per patient is included, and which BSI definition is used, can all affect the results.1,17,18 The latter is especially important in studies where higher rates of BSI caused by skin commensals are reported, as in our study. For BSI episodes where CoNS are likely to represent true pathogens, at least two positive blood cultures should be met.1,9,10,18 Therefore, our high rate of CoNS BSI may be partly explained by difficulties in distinguishing true pathogens from contaminants in this patient population. When CoNS cases were excluded from the analysis, the incidence remained higher than in the UK survey (5.1 vs 2.9 per 100 admissions) suggesting that factors other than the interpretation of positive blood culture may have contributed to the high rate of BSI.15

Surveillance which took place during the outbreaks of S. marcescens and MRSA may have produced higher rates of BSI caused by these organisms compared with surveillance performed when there were no outbreaks. S. marcescens, which is a well-recognized cause of outbreaks, was the second most common pathogen in our study.2,10

The patient:nurse ratio (3:1) can affect adherence to infection control measures and may have played a role in the CL-associated BSI rate.20

The distribution of infecting organisms (except for S. marcescens) was similar to other studies conducted in NICU and PICU.3,11–17

Although our numbers are small, antimicrobial resistance was encountered because of the clonal spread of the outbreak strains. These resistance data do not reflect the reported epidemiology of antimicrobial resistance in Estonia (www.ecdc.europa.eu/en/activities/surveillance/EARS-Net).

By contrast with studies where invasive Candida infections are a major cause of morbidity and mortality in preterm neonates, this pathogen was rare in our study.21 This observation could in part be explained by the use of prophylactic fluconazole in high-risk neonates and a conservative approach to empiric antibiotics.

Our overall BSI case-fatality rate (10%) and the case-fatality rate within 7 days of the first positive blood culture (1%) are lower than those reported by Gray et al. for patients in PICU (26.5% and 10.7%, respectively).11 In US studies of paediatric patients and VLBW neonates the overall BSI mortality was 14% and 18%, respectively.16,22 The high rate of CoNS infections, which have a lower mortality, could also help explain the observed mortality in this study.16,22

In conclusion, we observed higher rates for BSIs in an Estonian mixed PICU than those reported in other studies and observed high levels of antimicrobial resistance, partly because of outbreaks. Future research should focus on the effects of infection control guideline implementation to prevent outbreaks and to decrease the relatively high incidence of CL-associated BSI. Distinguishing between contaminants and true pathogens remains a challenge that must be addressed to avoid the over-reporting of BSIs caused by skin commensals. Presenting the BSI rates with and without CoNS may provide more comparable data for benchmarking.

Conflict of interest statement
None declared.

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None.

References


