Pathogen-Specific Clustering of Nosocomial Blood Stream Infections in Very Preterm Infants

Felix Reichert, MD, Brar Piening, MD, Christine Geffers, MD, Petra Gastmeier, MD, Christoph Bührer, MD, Frank Schwab, PhD

BACKGROUND AND OBJECTIVES: Nosocomial infections in NICUs tend to cluster, sometimes as devastating outbreaks, but pathogen-specific transmission probabilities are unknown. We aimed to quantify the pathogen-specific risk of a blood stream infection (BSI) in preterm infants after an index case with that pathogen in the same department.

METHODS: Data of 44,818 infants below 1500 g birth weight of the German NICU surveillance system (2000–2011) were used to calculate the probability of a BSI in the presence or absence of another infant in the same unit with a same-pathogen BSI.

RESULTS: The relative risk was similar for the more common pathogens, Enterococcus spp (4.3; 95% confidence interval: 2.7–6.9; n = 243), Enterobacter spp (7.9, 5.4–11.4; n = 246), Escherichia coli (7.9; 5.1–12.1; n = 210), Candida albicans (8.7; 5.0–15.4; n = 138), Staphylococcus aureus (9.5; 7.6–12.1; n = 407) and Klebsiella spp (13.1; 9.0–19.1; n = 190) but markedly elevated for Serratia spp (77.5; 41.1–146.1; n = 58) and Pseudomonas aeruginosa (64.5; 25.7–162.1; n = 38). Rates of BSI per 100 exposed infants ranged between 2.21 (Enterococcus) and 8.15 (Serratia). The same pattern emerged after adjustments were made for patients’ characteristics or when the analysis was restricted to positive blood cultures during the preceding 30 days.

CONCLUSIONS: Although BSIs with P. aeruginosa or Serratia spp in preterm infants are rare, they are associated with a markedly elevated risk of secondary same-pathogen BSI and should prompt intensified active surveillance and infection control measures.

WHAT’S KNOWN ON THIS SUBJECT: Nosocomial infections in neonatal intensive care tend to run in clusters. Calculating pathogen-specific transmission probabilities requires large databases.

WHAT THIS STUDY ADDS: The relative risk for a same-pathogen blood stream infection after an index case in the same unit is markedly elevated for Pseudomonas aeruginosa and Serratia spp, as compared with other pathogens.

In very low birth weight preterm infants, nosocomial blood stream infections (BSIs) are associated with substantial morbidity and mortality. BSI with the most commonly isolated organisms in BSI, coagulase-negative staphylococci (CoNS) display a rather benign clinical course.\(^1\) CoNS are part of the normal skin flora, and rates of BSI with CoNS have been found to decline after implementation of improved handling of central venous lines.\(^2,3\) In contrast, BSIs with Staphylococcus aureus, gram-negative rods, or fungi have a high mortality risk,\(^4\) with Pseudomonas aeruginosa and Serratia marcescens figuring prominently.\(^2,3,5,6\) Horizontal transmissions of these pathogens in NICUs may cause difficult-to-control outbreaks.

BSIs and outbreaks with non-CoNS pathogens, while potentially devastating for the affected infants or units, respectively,\(^7–11\) still occur mostly in a sporadic fashion. Thus, there is a need for a sufficiently large database to calculate and compare the BSI clustering probability for specific pathogens. We used the data from the German national neonatal infections surveillance system\(^1–10,12,13\) to estimate the probability of a hospitalized very low birth weight (<1500 g) infant to develop a BSI with a particular pathogen when another infant previously diagnosed with a BSI of the same pathogen was being cared for in the same unit. We also calculated the probability of contracting a BSI with a particular pathogen after an index case during the preceding 30 days in the same department.

**METHODS**

Methods and definitions employed by the German national neonatal infection surveillance system have been described previously.\(^1,10\) It has become the preferred surveillance system for neonatal nosocomial infections after participation in an infection surveillance system was made mandatory for all NICUs in Germany caring for infants below 1500 g birth weight. All analyses are done using anonymized data within the legal framework of quality improvement, obviating the need for ethical approval and informed consent.

The surveillance records pneumonia, necrotizing enterocolitis, and BSI beyond 72 hours of age in all preterm infants with a birth weight <1500 g until discharge, until death, or until they reach 1800 g. Trained hospital nurses and physicians collect demographic and obstetric data of all infants surveyed, and an array of clinical data of infected neonates.\(^12\) Non-CoNS BSIs are being defined as any case with a positive blood and/or cerebrospinal fluid culture with a recognized pathogen, unrelated to an infection at another site, in the presence of at least 2 clinical signs of systemic infection (increased [>38°C] or decreased [<36.5°C] body temperature or temperature instability, tachycardia, increased rates of apnea/bradycardia episodes, prolonged capillary refill, metabolic acidosis, hyperglycemia, apathy, or seizures). Pathogens isolated from cerebrospinal fluid are included in the BSI definition as most cases of meningitis in preterm infants result from hematogenous dissemination, and microbiological findings in cerebrospinal fluid may identify pathogens missed when culturing inadequate amounts of blood.

For the purpose of this analysis, exposure to a particular pathogen was defined in 2 ways:

1. An infant was considered exposed to a pathogen if a BSI with that particular species had caused a BSI in another infant (index case) cared for simultaneously in the same department (date of admission of the exposed infant preceding the date of discharge of the index case, date of BSI of the index case preceding the date of discharge of the exposed infant, and date of BSI of the index case preceding the date of BSI of the exposed infant).

2. An infant was considered exposed to a pathogen if a BSI with that particular species had been diagnosed in an index case cared for in the same department during the length of stay of the exposed infant or up to 30 days before admission of the exposed infant, with the date of BSI of the index case preceding the date of BSI of the exposed infant.

The analysis was restricted to pathogens implicated in >30 BSIs during the study period. As CoNS are part of the normal skin flora of virtually every infant and often considered contaminations when grown from blood cultures, no calculations were carried out for CoNS.

**Statistical Methods**

For the various pathogens, adjusted odds ratios (ORs) were calculated by using multivariable logistic regression models. The patient-based parameters birth weight (<500/500–749/750–999/1000–1249/1250–1499 g), gestational age (≤26/27–28/29–30–31 weeks), gender (boy/girl), delivery mode (planned cesarean, vaginal delivery, emergency cesarean), multiple birth (no/yes), and length of stay were considered in all models as confounders. Missing values were considered as a separate category. Furthermore, generalized estimating equations (GEEs) were calculated to consider clustering effects within a department by exchangeable correlation structure. In the GEE models, only birth weight and gender were considered in all models because the limited number of events restricted adjusting for more confounders.

\(P\) values < .05 were considered significant. Calculations were carried out using SPSS 22.0 (IBM SPSS).
### TABLE 1

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of BSI</th>
<th>Infants exposed, n (%)</th>
<th>Number of BSI in Exposed Infants</th>
<th>Rate of BSI per 100 Exposed Infants (95% CI)</th>
<th>RR (95% CI) Logistic Regression</th>
<th>Logistic Regression Adjusted OR (95% CI)</th>
<th>GEE Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>407</td>
<td>1172 (2.6)</td>
<td>83</td>
<td>7.08 (5.72–8.66)</td>
<td>9.54 (7.55–12.08)</td>
<td>7.96 (6.11–10.37)</td>
<td>6.90 (4.83–9.86)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>243</td>
<td>859 (1.9)</td>
<td>19</td>
<td>2.21 (1.38–3.37)</td>
<td>4.34 (2.73–6.90)</td>
<td>2.41 (1.59–3.67)</td>
<td>3.08 (2.13–4.38)</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>246</td>
<td>805 (1.8)</td>
<td>31</td>
<td>3.85 (2.89–5.36)</td>
<td>7.88 (5.85–11.41)</td>
<td>5.32 (3.59–7.91)</td>
<td>4.89 (2.66–9.20)</td>
</tr>
<tr>
<td>Eikenella cholera</td>
<td>210</td>
<td>689 (1.5)</td>
<td>23</td>
<td>3.34 (2.13–4.88)</td>
<td>7.88 (5.14–12.07)</td>
<td>4.58 (2.91–7.20)</td>
<td>4.26 (2.01–8.94)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>190</td>
<td>659 (1.5)</td>
<td>31</td>
<td>4.70 (3.29–6.53)</td>
<td>15.08 (8.96–25.05)</td>
<td>8.82 (5.84–13.31)</td>
<td>7.21 (5.23–12.02)</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>210</td>
<td>689 (1.5)</td>
<td>23</td>
<td>3.34 (2.13–4.88)</td>
<td>7.88 (5.14–12.07)</td>
<td>4.58 (2.91–7.20)</td>
<td>4.26 (2.01–8.94)</td>
</tr>
<tr>
<td>Serratia</td>
<td>190</td>
<td>659 (1.5)</td>
<td>31</td>
<td>4.70 (3.29–6.53)</td>
<td>15.08 (8.96–25.05)</td>
<td>8.82 (5.84–13.31)</td>
<td>7.21 (5.23–12.02)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>38</td>
<td>105 (0.2)</td>
<td>5</td>
<td>4.76 (1.77–10.24)</td>
<td>64.52 (25.69–162.05)</td>
<td>35.32 (12.71–98.20)</td>
<td>33.75 (7.02–162.17)</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>138</td>
<td>527 (1.2)</td>
<td>13</td>
<td>2.47 (1.38–4.08)</td>
<td>7.84 (4.97–15.37)</td>
<td>3.69 (2.03–6.69)</td>
<td>4.37 (2.35–8.14)</td>
</tr>
</tbody>
</table>

a Methicillin-sensitive.
b Vancomycin-sensitive.
c Cefotaxime-sensitive.

If a same-pathogen BSI was being cared for in the unit when a same-pathogen BSI had been diagnosed in the preceding 28 days in the same department, the risk (RR) for acquiring a BSI in the same department varied between 2.4 (Enterococcus spp) and 7.7 (Enterococcus faecalis). Adjusted ORs did not differ substantially with logistic regression analysis, adjusted ORs varied between 2.4 (Enterococcus spp) and 7.7 (Enterococcus faecalis) adjusted ORs. A previous study by our team (14) reported that infants caring for a particular pathogen in the neonatal department had a 30% probability of being exposed to a particular pathogen in a neonatal department within 30 days after that pathogen was isolated from a blood culture in another infant cared for in the unit. The probability of contracting a BSI with a particular pathogen was 2% higher in infants with a particular pathogen in the neonatal department. The same pattern emerged when calculating the probability of contracting a BSI with a particular pathogen in the unit. There was no difference in the probability of contracting a BSI with a particular pathogen in the unit when a same-pathogen BSI was occurring in the same department.

### RESULTS

Records of 44,181 infants with a birth weight <1500 g born between January 1, 2000, and December 31, 2011, and being cared for in 229 hospitals across Germany revealed 84,044 BSI. Pathogens identified (in descending order) were Staphylococcus aureus (59.5%), vancomycin-sensitive Enterococcus spp (28.2%), and 38.1% (77.5%) of the infants were born between 28 and 31 weeks of gestation. The likelihood of identical hospital-acquired BSIs (AABB) and Group B Streptococcus (GBS) was 1.3% (SAS Institute, Inc, Cary, NC).

There are several limitations to this study. First, the reporting system made no distinction between various strains of Enterococcus, Enterobacter, or Serratia, and there was no genotyping of the pathogens involved. Thus, there are no overlapping 95% confidence intervals (CIs). The first CIs contains the second group comprises Enterobacter spp and K. pneumoniae. Whereas the second group comprises Acinetobacter baumannii (a = 28). Enterobacter aerogenes (a = 21), Enterobacter cloacae (a = 21), Enterobacter aerogenes (a = 21), and Enterobacter cloacae (a = 21). Adjusted ORs using logistic regression analysis or GEE are shown in Table 2.
### Table 2: BSI in the Presence of Absence of a Same Pathogen-BSI in the Same Department During the Preceding 30 d

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of BSI</th>
<th>Infants Exposed, n (%)</th>
<th>Number of BSI in Exposed Infants</th>
<th>Rate of BSI per 100 Exposed Infants (95% CI)</th>
<th>RR (95% CI)</th>
<th>Logistic Regression Adjusted OR (95% CI)</th>
<th>GEE Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>407</td>
<td>1115 (2.5)</td>
<td>53</td>
<td>4.75 (3.62–6.13)</td>
<td>5.87 (4.42–7.78)</td>
<td>4.50 (3.31–6.12)</td>
<td>3.58 (2.28–5.83)</td>
</tr>
<tr>
<td>Enterococcus spp&lt;sup&gt;b&lt;/sup&gt;</td>
<td>243</td>
<td>814 (1.8)</td>
<td>10</td>
<td>1.23 (0.63–2.18)</td>
<td>2.32 (1.24–4.39)</td>
<td>1.69 (0.79–3.62)</td>
<td>1.39 (0.78–2.48)</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>246</td>
<td>882 (2.0)</td>
<td>26</td>
<td>2.95 (1.94–4.23)</td>
<td>5.89 (3.94–8.79)</td>
<td>4.45 (2.91–6.79)</td>
<td>3.99 (2.07–7.7)</td>
</tr>
<tr>
<td>Escherichia coli&lt;sup&gt;c&lt;/sup&gt;</td>
<td>210</td>
<td>853 (1.9)</td>
<td>90</td>
<td>2.95 (1.94–4.23)</td>
<td>5.89 (3.94–8.79)</td>
<td>4.45 (2.91–6.79)</td>
<td>3.99 (2.07–7.7)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae&lt;sup&gt;d&lt;/sup&gt;</td>
<td>190</td>
<td>764 (1.8)</td>
<td>32</td>
<td>2.06 (1.26–3.37)</td>
<td>4.12 (2.38–7.02)</td>
<td>3.05 (1.57–5.91)</td>
<td>2.67 (1.39–4.36)</td>
</tr>
<tr>
<td>Serratia spp</td>
<td>246</td>
<td>882 (2.0)</td>
<td>26</td>
<td>2.95 (1.94–4.23)</td>
<td>5.89 (3.94–8.79)</td>
<td>4.45 (2.91–6.79)</td>
<td>3.99 (2.07–7.7)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>38</td>
<td>109 (0.3)</td>
<td>10</td>
<td>6.52 (3.33–13.6)</td>
<td>59.47 (29.80–118.67)</td>
<td>47.83 (22.0–104.04)</td>
<td>24.68 (3.76–162.15)</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>138</td>
<td>445 (1.0)</td>
<td>6</td>
<td>3.67 (1.18–8.61)</td>
<td>35.82 (11.19–114.7)</td>
<td>25.27 (8.39–76.05)</td>
<td>24.68 (3.76–162.15)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Methicillin-sensitive.  
<sup>b</sup> Vancomycin-sensitive.  
<sup>c</sup> Cefotaxime-sensitive.

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The differences between the pathogens analyzed for involvement in neonatal infections may be influenced by different and local prevalences of pathogens. As S. aureus and S. marcescens have been identified as reservoirs for CoNS during the first week of life, the colonization of the infant's skin with CoNS may turn into an invasive disease usually triggered by skin infections to colonizations are 1:6 for CoNS, as virtually all preterm infants acquire bacterial conjunctivitis, and all infants positive for a certain pathogen, have been reported to be over 20% for P. aeruginosa<sup>c</sup> and S. marcescens<sup>c</sup>. The reported rates of CoNS from the blood culture of a sick infant indicates the contagiousness of a pathogen but the rate of BSI may reflect differences of the clinical symptoms of systemic infection.21 or infected infants without clinical manifestations may involve chains of colonized infants who are not subjects to this type of infection surveillance. Fourth, the analysis was restricted to very low birth weight infants, but NICUs are being populated also by more mature infants being cared for in the same department may or may not have shared the same room. Third, the proximity of infants contracting BSI with the same pathogen. In addition to transmission via the hands of staff, pathogens have been found to figure prominently in NICU environment, or both. It may also spread from patient-to-patient spreading in this environment. The rate of BSI in exposed infants was also usually not present in hospitalized preterm infants and the advent of a culture of a sick infant indicates the contagiousness of a pathogen but the rate of BSI may reflect differences of the clinical symptoms of systemic infection.21 or infected infants without clinical manifestations may involve chains of colonized infants who are not subjects to this type of infection surveillance. Fourth, the analysis was restricted to very low birth weight infants, but NICUs are being populated also by more mature infants being cared for in the same department may or may not have shared the same room. Third, the proximity of infants contracting BSI with the same pathogen. In addition to transmission via the hands of staff, pathogens have been found to figure prominently in NICU environment, or both. It may also spread from patient-to-patient spreading in this environment. The rate of BSI in exposed infants was also usually not present in hospitalized preterm infants and the advent of a
The authors have indicated they have no potential conflicts of interest to disclose.

POTENTIAL CONFLICT OF INTEREST:
Charité University Medical Center.

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ABBREVIATIONS
BSI: blood stream infection
CI: confidence interval
CoNS: coagulase-negative staphylococci
GEE: generalized estimating equation
OR: odds ratio
RR: relative risk

CONCLUSIONS

P aeruginosa and Serratia spp are exceptional in their potential to spread in the NICU and attack very low birth weight infants. Because they are also those pathogens with the highest reported BSI-related mortality rates, vigorous attempts should be made to intensify infection control measures whenever P aeruginosa or Serratia spp have been isolated from a patient in the NICU.

REFERENCES


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