The epidemiology of recurrent Gram-negative bacteremia in a tertiary-care hospital

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Abstract

We examined recurrent Gram-negative bacteremia in a prospective cohort from a tertiary hospital. Seventeen (7.1%) of 241 bacteremic patients developed recurrence (median time to recurrence = 44 days; range, 9–217 days). Recurrent and nonrecurrent bacteremic patients did not differ in clinical characteristics and mortality.

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In the United States, approximately 250 000 episodes of bloodstream infections occur annually, causing substantial morbidity and mortality (Pittet and Wenzel, 1995). Recurrence of bloodstream infections is a recognized complication, particularly among Staphylococcus aureus bacteremias (Capdevila et al., 1994; Chang et al., 2003; Fowler et al., 1999; Johnson et al., 2003; Kreisel et al., 2006; Siegman-Igra et al., 2005), where it is associated with retained indwelling devices (Fowler et al., 1998; Johnson et al., 2003) and inferior antibiotic therapy (Chang et al., 2003; Fowler et al., 1999; Siegman-Igra et al., 2005). Gram-negative bacteremias account for approximately 25% to 27% of bloodstream infections (Edmond et al., 1999; Wisplinghoff et al., 2004); however, little is known about the epidemiology of recurrent Gram-negative bacteremia (Mylotte and McDermott, 1988; Wendt et al., 1999b). Wendt et al. associated recurring Gram-negative bacteremia with intravascular catheters and an inadequate duration of antibiotic treatment. Mylotte and McDermott (1988) found an association between underlying malignancy and recurrence.

Our objective was to prospectively determine the rate of recurrence of Gram-negative bloodstream infections in hospitalized patients and describe risk factors associated with recurrence. We performed a prospective cohort study of patients with Gram-negative bacteremia at Barnes-Jewish Hospital, St. Louis, MO, a 1250-bed teaching hospital, during a 6-month period between August 1, 2006, and January 31, 2007. We received daily electronic notification of patients with ≥1 blood culture positive for Gram-negative bacteria. Bacteremic adult patients housed in acute care inpatient wards were included. Bacteremic patients who were never admitted (e.g., positive blood culture from emergency department visit without admission) were excluded. Blood cultures were processed using BACTEC 9240 (Becton-Dickinson Diagnostic Systems, Sparks, MD). The disk-diffusion method was used for antibiotic susceptibility testing.

Patient medical records were reviewed for demographics and medical history. Charlson comorbidity (Charlson et al., 1987) and McCabe severity of illness (McCabe and Jackson, 1962) scores were computed. Patients’ vital signs and laboratory and pharmacy data were continuously reviewed during the admission. Recurrence of bacteremia was defined as repeated detection of Gram-negative bacteria in a blood culture after ≥1 negative blood culture and after an interval of >7 days, similar to Wendt et al. (1999b). Relapse (i.e., repeat bacteremia with the same strain) versus reinfection...
(i.e., detection of a different strain) was determined by speciation and susceptibility patterns (Wendt et al., 1999b). Inadequate empiric antibiotic treatment was defined as no antibiotic or an antibiotic to which the organism was not susceptible, administered within 24 h of when the blood cultures were drawn. Community-acquisition of bacteremia was defined as bacteremia occurring within 48 h of admission. Microbiologic data for the included patients were collected through July 31, 2007, to ensure that all had ≥6 months of follow-up.

Data were collected using Microsoft Access and Excel (Microsoft, Redmond, WA) and analyzed using SPSS 14 (SPSS, Chicago, IL). Univariate comparisons among categoric variables were performed using the χ² test or Fisher’s exact test as appropriate. Comparisons among continuous independent variables were performed using Student’s t test or Mann–Whitney U test as appropriate. A 2-sided P value of <0.05 was considered significant. Because of the small number of patients with recurrent bacteremia, multivariate logistic regression analysis could not be performed.

The Washington University Human Research Protection Office approved the study.

Seventeen (7.1%) of 241 patients with Gram-negative bacteremia had recurrent bacteremia during the study period. The median time to recurrence was 44 days (range, 9–217 days) (Table 1). Five patients had recurrent Gram-negative bacteremia during the same admission; 12 had recurrence during a subsequent admission. The predomi-
nant bacteria recovered in recurrent bacteremia were Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa, in a frequency of occurrence similar to single-episode bacteremias (E. coli, 5 [29.4%] recurrent versus 53 [23.7%] single-episode bacteremia, P = 0.6; K. pneumoniae, 5 [29.4%] versus 41 [18.3%], P = 0.3; and P. aeruginosa, 3 [17.6%] versus 16 [7.6%]; P = 0.2). Ten (58.8%) of 17 patients with recurrent infection had bacteremia caused by Gram-negative bacteria different from the organism causing the first episode (i.e., reinfection), and 7 patients (41.2%) had recurrences of the same organism; in 6 of these cases, the organism had an identical antimicrobial susceptibility pattern (i.e., relapse). In the 3 E. coli relapses, the total duration of antibiotic treatment was 4, 5, and 10 days, respectively. The duration of antibiotic treatment for the initial episodes of non-E. coli bacteremias was 12, 28, and 35 days, respectively (Table 1). In 2 (33.3%) of 6 relapsing bacteremias, a central venous catheter was not removed until the time of recurrence. None of the 17 patients were diagnosed with endocarditis.

We compared 17 patients with recurrent bacteremia with 224 patients with a single episode of infection (Table 2). No significant differences in patient characteristics, comorbidities, or potential risk factors were seen. Liver disease was more frequently encountered in patients with recurrent bacteremia; however, this difference did not reach statistical significance. A possible explanation is the increased incidence of bacteremias in cirrhotic patients, which is

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Microorganism, first episode</th>
<th>Microorganism, second episode</th>
<th>Interval (days)</th>
<th>Duration and type of antibiotic treatment, during first episode (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P. aeruginosa</td>
<td>P. aeruginosa</td>
<td>12</td>
<td>12, ciprofloxacin</td>
</tr>
<tr>
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<td>K. pneumoniae,</td>
<td>K. pneumoniae</td>
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<td>35, piperacillin/tazobactam</td>
</tr>
<tr>
<td>3</td>
<td>E. coli, P. aeruginosa, GPB</td>
<td>Alcaligenes xylosoxidans</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>Enterobacter cloacae</td>
<td>Aeromonas sp.</td>
<td>62</td>
<td></td>
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<tr>
<td>5</td>
<td>Acinetobacter baumannii and GPB</td>
<td>A. baumannii and GPB</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
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<td>A. baumannii and GPB</td>
<td>E. coli</td>
<td>27</td>
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<td>Stenotrophomonas maltophilia and Pseudomonas fluorescens</td>
<td>A. xylosoxidans</td>
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<td>Citrobacter koseri</td>
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<td>P. aeruginosa</td>
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<td>P. aeruginosa</td>
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<tr>
<td>17</td>
<td>E. coli</td>
<td>E. coli</td>
<td>85</td>
<td>10, cefepime, ciprofloxacin</td>
</tr>
</tbody>
</table>

GPB = Gram-positive bacteria.

* Duration of treatment is not given for recurrence with a different species (i.e., reinfection). Patient 5 had recurrence with the same species but exhibited a different antimicrobial susceptibility pattern. Patient 1 had bacteria that were pansusceptible. Patient 2 had bacteria resistant only to ampicillin. Patient 7 had bacteria resistant to ampicillin, ciprofloxacin, and Bactrim. Patient 8 had bacteria resistant to ampicillin and Bactrim and intermediate to cefazolin. Patient 11 had bacteria resistant to ampicillin, gentamicin, Bactrim, and ciprofloxacin. Patient 17 had bacteria that were pansusceptible.

b Denotes recurrence during the same admission.
thought to be a consequence of bacterial translocation (Guarner and Soriano, 2005). There was no difference in in-hospital mortality (3 [17.6%] versus 34 [15.2%], \( P = 0.7 \)).

Recurrence of Gram-negative bacteremia is uncommon. The rate of recurrence we found in our prospective cohort of hospitalized patients (7.1%) was similar to the 7.1% to 9.8% rate reported in older studies (Mylotte and McDermott, 1988; Wendt et al., 1999b). Whereas the molecular analysis of bacterial isolates from recurrent bacteremia in 1 study showed that 65% were due to relapses with the same strain (Wendt et al., 1999a), in our cohort, the majority of recurrences were reinfections caused by different species. Wendt et al. (1999b) proposed to define all positive blood cultures recovered during an arbitrary period of 7 days as 1 episode. In our study, 4 relapses of bacteremia occurred within 1 to 5 days, and 3 of these patients did not receive antibiotics at all (data not shown), probably because of a low initial suspicion for bacteremia. Therefore, these “relapses” more likely represented persistent bacteremia, for which inappropriate treatment has been described as a risk factor (Chowers et al., 2003), and they were not considered recurrences.

Hanna et al. (2004) demonstrated that failure to remove an intravascular catheter was associated with increased risk of relapsing infection in catheter-related Gram-negative bacteremia. Similar findings were observed in patients with hemodialysis catheters (Mokrzycki et al., 2006). In our study, the intravascular catheter was retained in 2 (33%) of the relapsing bacteremias. A much more important risk factor for recurrent infection is likely an inappropriate duration of antibiotic treatment (Wendt et al., 1999b), because all 3 \( E. coli \) relapses in our study were treated for \( \leq 10 \) days. We did, however, not compare duration of treatment in recurrent versus nonrecurrent bacteremia.

The small number of recurrent bacteremias and the single-center setting are other limitations of our study. There is also potential ascertainment bias because some patients may have presented to outside hospitals with recurrent episodes of bacteremia.

In summary, we found that recurrence of infection is an infrequent aspect of Gram-negative bacteremia that is not associated with an increased mortality rate compared to single-episode bacteremias. We could not elic it any risk factors predisposing to recurrence of bacteremia.

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References


