Five years of nosocomial Gram-negative bacteremia in a general intensive care unit: epidemiology, antimicrobial susceptibility patterns, and outcomes

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Intensive care;
Nosocomial infection

Summary
Objectives: Nosocomial Gram-negative bacteremia in the critically ill is associated with significant morbidity and mortality. This study provides epidemiological and antimicrobial susceptibility data for nosocomial Gram-negative bacteremia in a general intensive care unit (ICU) over a five-year period.

Methods: Positive blood cultures from January 1, 1999 to December 31, 2003 were reviewed for microbial etiology and susceptibilities. Patient charts were reviewed to determine the source of infection and outcome.

Results: Forty-five nosocomial Gram-negative bacteremias occurred in 44 patients. Infection rates of 6.9/1000 admissions and 11.3/10 000 patient days remained stable. Admitting diagnoses included respiratory failure, solid organ transplant, post-surgery, and multi-trauma. Seven bacterial species were identified; \textit{Pseudomonas aeruginosa} and \textit{Enterobacter spp} were most common. Sources of bacteremia included pneumonia (48.9%), and central venous catheterization (22.2%). Antimicrobial susceptibilities were highest for imipenem, gentamicin, tobramycin, ceftriaxone, and piperacillin–tazobactam. Ciprofloxacin susceptibility was inferior to imipenem, gentamicin, and tobramycin ($p \lt 0.05$). Mortality rates were 53.3% in the ICU, and 60% for overall hospitalization. Average length of ICU stay was 50.5 days compared to 6.13 days for all-comers.

Conclusions: Nosocomial Gram-negative bacteremia is associated with marked morbidity and mortality in critically ill patients. Significant resistance to ciprofloxacin was demonstrated. Empiric treatment regimens should be based on unit-specific data.

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Introduction

Nosocomial bacteremia is a major subgroup of hospital-acquired infections. Gram-negative bacteremia, in particular, is associated with significant morbidity and mortality. Studies of Gram-negative bacteremia provide epidemiological data, and may improve empiric antimicrobial therapy based on local patterns of susceptibility. Such information may also lead to infection control measures designed to decrease infection rates.

Intensive care unit (ICU) patients are at higher risk of developing nosocomial infections when compared with other hospitalized patients. Incidence of nosocomial bacteremia in ICU patients has been reported from 1% to as high as 6.5%, compared to 0.65% in other hospitalized patients. Furthermore, a recent epidemiologic study showed that ICU patients represented 34% of all hospital Gram-negative bacteremias. Patients with Gram-negative bacteremia have a high mortality rate. In a study from a large Swiss university hospital, there was a 7-fold higher death rate compared to hospitalized patients without Gram-negative bacteremia. In addition, Gram-negative bacteremia in the setting of critical illness, as determined by admission to ICU, has been associated with higher mortality rates and prolonged ICU stay.

The mortality rate in a study of Gram-negative sepsis in five ICUs in Taipei was 36.1%, with 77.4% of all deaths directly related to the bloodstream infection. Furthermore, Gram-negative bacteremias have been associated with higher case fatality rates when compared to Gram-positive bacteremias (44% vs. 30%). In short, Gram-negative bacteremia has a significant impact on patient mortality, morbidity, and resource utilization.

The purpose of this study is to provide up-to-date data on the frequency, source, microbial etiology, and susceptibilities of Gram-negative bacteremia, with the goal of improving its management. This is the first Canadian study of nosocomial Gram-negative bacteremia in a general ICU, and we hope to emphasize the importance of frequent surveillance for both nosocomial infections and increasing antimicrobial resistance.

Methods

The University of Alberta Hospital is a 700-bed tertiary referral hospital in Edmonton, Canada. It is the principal teaching hospital of the University of Alberta, Faculty of Medicine. It is a level-one trauma center, and has a referral area of over two million people. It includes a 29-bed adult ICU that admits general medical, trauma, and surgical patients, as well as solid organ transplant recipients. The ICU provides invasive hemodynamic monitoring and support, mechanical ventilation, and continuous renal replacement therapy. Under usual circumstances, cardiovascular surgery, neurosurgical/neurological, and burn patients requiring intensive care are not admitted to the general unit, as there are separate dedicated ICUs for these patients.

Inpatient populations have been prospectively surveyed for nosocomial bloodstream infections since 1986 as part of our hospital’s routine infection control surveillance program. Positive blood cultures in ICU patients are identified by the clinical microbiology laboratory (BACTEC 9240 Blood Culture System; Becton Dickinson Biosciences) and reviewed daily. Charts are reviewed and the blood culture isolates are categorized as contaminated specimens, community-acquired infections, or nosocomial bacteremias using standardized criteria. Originating sources for nosocomial bacteremias are then identified according to standard CDC definitions.

All cases of aerobic Gram-negative bacteremia from January 1, 1999 to December 31, 2003 were reviewed. Demographic data, time from admission to bacteremia, causative organisms, antimicrobial susceptibilities, choice of empiric antibiotic therapy, ICU length of stay, and mortality rates were collected. For statistical analysis, differences in proportions for categorical variables were compared using the Chi-square test; for continuous variables the t-test was used.

Results

There were 6544 admissions to the general systems ICU from January 1, 1999 to December 31, 2003. Forty-five episodes of Gram-negative nosocomial bacteremia occurred in 44 patients, resulting in infection rates of 6.9 per 1000 ICU admissions and 11.3 per 10 000 patient days. Annual infection rates by year fluctuated from 3.0 to 11.1 per 1000 admissions and 4.9 to 19.2 per 10 000 patient days, with no overall increase in rates over the five-year period. The majority (95.6%) of bloodstream infections were monomicrobial, with only one episode of polymicrobial bacteremia. This polymicrobial bacteremia was analyzed as if it were two separate infections. The mean patient age was 55.3 years (range 17—86 years); 27.3% of patients were female, and 72.7% were male.

Admitting diagnoses included: respiratory failure (18.2%), post-surgery (15.9%; all were cancer-related surgeries), solid organ transplant (15.9%), multi-trauma (13.6%), hepatic failure (9.1%), intra-abdominal sepsis (9.1%), other sepsis (6.8%), decreased level of consciousness (4.5%), and other (6.8%, with one case each of gastrointestinal bleed, acute renal failure, and complications following burns). Ten patients (22.7%) were on corticosteroids or other immunosuppressive agents prior to admission to ICU (Table 1).

Sources of bacteremia (Table 2) included pneumonia (48.9% all but two of which were ventilator-associated), central venous catheter (22.2%), surgical site (15.6%), gastrointestinal (6.7%), skin (4.4%), and urinary tract infection (2.2%). There were no cases of primary bacteremia, or associations with ear/nose/throat infections or gastrointestinal endoscopy. Of the ten bacteremias due to central line infections, femoral catheters were used in five (50%), subclavian catheters in three (30%), and internal jugular catheters in two of the cases (20%).

Seven bacterial genera were identified in the 45 episodes of bacteremia (Table 2). These were Pseudomonas aeruginosa (22.2%), Enterobacter spp (22.2%; nine E. cloacae, one E. aerogenes), Klebsiella pneumoniae (17.8%), Escherichia coli (15.6%), Serratia marcescens (11.1%), Stenotrophomonas maltophilia (8.9%), and Acinetobacter anitratus (2.2%). Two patients had two strains of the same species; during our analysis these were analyzed separately for susceptibility data but included as only one episode of bacteremia.
Overall susceptibilities are shown in Table 3. Of the isolates, 98.5% were susceptible to imipenem, 94.6% to gentamicin, 93.3% to tobramycin, 92.4% to ceftazidime, 88.9% to piperacillin—tazobactam, 73.2% to ciprofloxacin, 72.0% to trimethoprim—sulfamethoxazole (TMP—SMX), and 62.1% to piperacillin alone. Imipenem, tobramycin, and gentamicin were superior to ciprofloxacin ($p$ values 0.0013, 0.0045, and 0.0055, respectively), with a trend towards ceftazidime and piperacillin—tazobactam superiority that was not statistically significant ($p$ values 0.064 and 0.12, respectively).

There was also a trend towards imipenem superiority compared to piperacillin—tazobactam, but this was not statistically significant ($p = 0.11$).

All four strains of *Stenotrophomonas maltophilia* were susceptible to TMP—SMX, and resistant to ticarcillin—clavulanate, minocycline, and amikacin. None of these patients received initial empiric therapy with TMP—SMX, but all were treated with TMP—SMX once susceptibilities were reported.

Data were collected on the choice of empiric therapy after preliminary Gram-stain results were known. Three patients were not treated due to compassionate care limitations. For one episode, susceptibility of the organism to the empiric antibiotic was not tested. After excluding these four episodes, 80.5% of bacteremias were treated with an agent to which the microorganism was ultimately susceptible. After excluding the four cases of *Stenotrophomonas maltophilia*, for which empiric therapy is currently not standard of care, empiric coverage increased to 89.2%.

ICU length of stay and median time to bacteremia was calculated for all patients. If there were multiple ICU admissions, the discrete ICU admission surrounding the bacteremia was used. In three cases, multiple transfers to and from the ICU meant that no discrete ICU admission could be identified. As such, the entire hospitalization was counted. The median time from admission to hospital to development of bacteremia was 18.5 days (mean 32.9 days, 95% confidence interval (CI) 0—100.9), and time from admission to ICU was 15.0 days (mean 26.0 days, 95% CI 0—90.1). The median length of stay for study patients was 39.0 days (mean 50.5 days, 95% CI 0—150.1). In comparison, the median length of stay for all—comers to the ICU over the same five—year period was 6.16 days (mean 6.13 days, 95% CI 4.29—7.97).

Mortality rates for patients with nosocomial Gram-negative bacteremia were 53.3% in the ICU and 60% over the entire hospitalization. This compares to an overall mortality rate of 11.72% for the year 2004 in our ICU patients (five—year data were not available). After excluding cases of *Stenotrophomonas*, when empiric antimicrobial therapy was appropriate, the mortality rate over the entire hospitalization was 59.4%. When empiric therapy was not effective, requiring a change of therapy after susceptibilities were reported, mortality was 100%. Median lengths of stay were 41 and 69 days, respectively, for those who did and did not receive appropriate empiric therapy.

### Table 2: Microorganisms isolated by source

<table>
<thead>
<tr>
<th>Organism</th>
<th>Site</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PN</td>
<td>CVC</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>22</td>
<td>(48.9)</td>
</tr>
<tr>
<td><em>Enterobacter spp</em></td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><em>Acinetobacter anitratus</em></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

PN: pneumonia; CVC: central venous catheter; SSI: surgical site infection; GI: gastrointestinal; UTI: urinary tract infection.
documented in the literature. Previous studies of nosocomial bacteremia in ICU patients report rates of 6.0 and 20.0 per 1000 admissions, however Gram-negative bacteria comprised only 53% and 11% of the isolated microorganisms, respectively.\textsuperscript{4,5} Wisplinghoff et al., in an analysis of 24,179 nosocomial bloodstream cases in a prospective multi-center USA surveillance study, reported a lower Gram-negative nosocomial bloodstream infection rate of 1.1 per 1000 admissions, however this included all hospitalized patients, not ICU patients alone.\textsuperscript{11} The median time from admission to the development of bacteremia in our study was 18.5 days. Wisplinghoff et al. reported shorter mean times from 12 to 26 days in Gram-negative bacteremia.\textsuperscript{11}

The most common organisms isolated were \textit{Pseudomonas aeruginosa} and \textit{Enterobacter} spp. Similar studies of nosocomial Gram-negative bacteremia in critically ill patients have reported \textit{Acinetobacter baumannii}, \textsuperscript{1,12} \textit{Pseudomonas}, \textsuperscript{11–13} and \textit{Enterobacter}\textsuperscript{14} most commonly. Interestingly, only one Acinetobacter bacteremia was observed in our study, reflecting the importance of collecting unit-specific data. A large European single-day point prevalence study of nosocomial ICU infections, reported Enterobacteriaceae as most common (34.4%), with \textit{Pseudomonas} second most common (28.7%). However, only 12% of these infections were bacteremias. Regardless, these data emphasize the large number of nosocomial Gram-negative infections in the critically ill.

The most common source of bloodstream infection in our study was pneumonia (48.9%) almost all of which was ventilator associated, followed by central venous catheter infection (22.2%). Previous studies have identified the lower respiratory tract\textsuperscript{1} and urinary tract\textsuperscript{2} as common sources of Gram-negative bacteremia. While intravenous catheters have been previously reported as a leading source of nosocomial bloodstream infections, the majority of these have been Gram-positive bacteremias,\textsuperscript{11} which were excluded from this study.

Providing epidemiologic data to guide empiric antimicrobial therapy is a major goal of this study. Inappropriate empiric therapy has been shown to predict death in critically ill patients.\textsuperscript{16,17} Higher rates of mortality were observed in patients who received inappropriate empiric antimicrobial therapy, although the small number of cases limits rigorous statistical analysis of the role of chance in this finding. In fact, mortality was 100% in all four cases of bacteremia in which empiric therapy was not appropriate.

\textit{Pseudomonas aeruginosa} was relatively fluoroquinolone-resistant, with only 54.5% susceptibility to ciprofloxacin. Several clinical and pharmacologic studies have suggested fluoroquinolone monotherapy or combination therapy for the treatment of ICU infections.\textsuperscript{18} However, the high risk of resistance selection is a concern, particularly in ICU, and is highlighted by our data. Rates of fluoroquinolone resistance among \textit{P. aeruginosa} are increasing; a recent study documented an increase from 29% in 1999 to 36% in 2001 associated with increases in hospital and community fluoroquinolone use.\textsuperscript{19} Furthermore, mortality is increased in ICU patients with \textit{P. aeruginosa} bacteremia and inadequate antimicrobial treatment.\textsuperscript{20} Recent National Nosocomial Infections Surveillance System (NNIS) data, comparing 1.3 million nosocomial bacterial infections from 1975 to 2003, indicate that rates of nosocomial infections due to Gram-negative bacilli are not increasing, but resistance to therapy is increasing, particularly in \textit{Pseudomonas} and \textit{Acinetobacter} species.\textsuperscript{21} This issue is particularly concerning given that no new antibiotics for resistant Gram-negative organisms are anticipated for at least five years.\textsuperscript{22}

The use of combination antibiotic therapy for Gram-negative bacteremia is controversial. A recent meta-analysis, comparing beta-lactam monotherapy with beta-lactam–aminoglycoside combination therapy for severe infections found no difference in all-cause fatality (relative risk 0.90, 95% CI 0.77–1.06).\textsuperscript{23} In addition, there was no advantage among patients with Gram-negative infections or \textit{P. aeruginosa} infections. Nephrotoxicity was, however, significantly more common with combination therapy.

A second meta-analysis\textsuperscript{24} reported no overall mortality benefit with combination therapy; however, analysis of \textit{P. aeruginosa} bacteremias alone did show a 50% mortality benefit. As such, the routine use of combination antibiotic therapy for Gram-negative bacteremia is not encouraged, beyond settings where infection by \textit{P. aeruginosa} is strongly suspected. If \textit{P. aeruginosa} is suspected, two-drug coverage with either an aminoglycoside or ciprofloxacin is recommended. In our unit, gentamicin and tobramycin provide reliable anti-pseudomonal coverage, but potential nephrotoxicity is a concern in the critically ill population. Ciprofloxacin, on the other hand, would provide coverage to barely half the \textit{P. aeruginosa} bacteremias in our unit. A potential compromise might be to give a single dose of aminoglycoside based on the initial report of Gram-negative bacteremia, and review treatment in 24–48 hours, when the identity and antimicrobial susceptibility of the isolate are available.

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
\textbf{Agent} & \textbf{Antimicrobial susceptibility by organism (%)} \\
 & \textit{Pseudomonas} & \textit{Enterobacter} & \textit{Klebsiella} & \textit{E. coli} & \textit{Serratia} & \textit{Acinetobacter} & \textbf{Total} \\
 & \textit{n = 11} & \textit{n = 11} & \textit{n = 8} & \textit{n = 7} & \textit{n = 5} & \textit{n = 1} & \textit{n = 43} \\
\hline
Ceftazidime & 81.8 & 72.7 & 100 & 100 & 100 & 100 & 92.4 \\
Ciprofloxacin & 54.5 & 90.9 & 62.5 & 71.4 & 60 & 100 & 73.2 \\
Gentamicin & 81.8 & 100 & 100 & 85.7 & 100 & 100 & 94.6 \\
Imipenem & 90.9 & 100 & 100 & 100 & 100 & 100 & 98.5 \\
Piperacillin & 81.8 & 72.7 & 75 & 42.9 & 100 & 0 & 62.1 \\
Piperacillin–tazobactam & 100 & 72.7 & 75 & 85.7 & 100 & 100 & 88.9 \\
Tobramycin & 100 & 100 & 100 & 100 & 60 & 100 & 93.3 \\
TMP–SMX & 9.1 & 100 & 100 & 100 & 100 & 100 & 72.0 \\
\hline
\end{tabular}
\caption{Antimicrobial susceptibility of blood culture isolates}
\end{table}

\textit{TMP—SMX}: trimethoprim–sulfamethoxazole.
Stenotrophomonas maltophilia represented nearly 10% of our isolates, highlighting the growing importance of this nosocomial pathogen. Empiric coverage is difficult as few agents are effective. In our study, isolates were susceptible only to TMP-SMX. Empiric use of TMP-SMX is problematic in light of its limited coverage of other organisms, and the large fluid volume required for administration. In addition, Stenotrophomonas maltophilia is an organism of low virulence and rarely a cause of acute clinical deterioration. As such, we do not recommend empiric TMP-SMX for patients with Gram-negative bacteremia in our ICU, but the incidence of S. maltophilia in this population needs to be monitored.

E. coli and Klebsiella can produce extended-spectrum beta-lactamas (ESBLs). ESBLs are widely prevalent in Latin America, with rates as high as 32.6% for K. pneumoniae and 11.8% for E. coli in the ICU. A large international prospective observational study of 12 hospitals identified 30.8% of all hospital nosocomial bacteremias and 43.5% of episodes acquired in ICUs were due to ESBL-producing organisms. We did not identify any ESBLs in our study, but these highly resistant strains may become more widespread in the future. Minimizing inappropriate antibiotic use, particularly with beta-lactams containing an oxyimino group, may help guard against the emergence of ESBLs, and is another reason why these data may help guide clinical decision-making.

Serratia marcescens and Enterobacter spp were responsible for 33.3% of bacteremias. Sensitivity to the third generation cephalosporins (ceftazidime, cefotaxime, ceftriaxone) was 100% for S. marcescens, and 66.6% for Enterobacter spp. However, Serratia and Enterobacter spp both have the potential to carry inducible cephalosporinases. This mandates caution when using cephalosporins empirically. Despite initial susceptibility, these organisms may quickly develop resistance.

Limitations of this study include the single center design, small numbers of bacteremia, and a short study period of five years. Inter-quartile and subset analyses were not possible due to these limitations.

In summary, this is the first Canadian study of nosocomial Gram-negative bacteremia in a general ICU. Pseudomonas aeruginosa and Enterobacter spp were identified as the most common organisms. Overall sensitivities to imipenem, tobramycin, and gentamicin were statistically superior to ciprofloxacin, demonstrating significant fluoroquinolone resistance. Ceftazidime and piperacillin—tazobactam were also highly active, with no statistically significant difference when compared to imipenem, gentamicin, or tobramycin. The potential for inducible cephalosporinase production in some organisms, however, makes ceftazidime a less attractive option for empiric therapy. If aminoglycosides are to be typically avoided in critically ill patients due to nephrotoxicity, then imipenem or piperacillin—tazobactam appear to be the antimicrobials most appropriate for empiric therapy in our intensive care unit. Local surveillance data should similarly be used to guide empiric therapy in other ICUs, and to ensure optimal therapy and resource allocation in the critically ill.

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Conflict of interest: No conflict of interest to declare.

References


