Predictive Factors for the Development of Central Line–Associated Bloodstream Infection Due to Gram-Negative Bacteria in Intensive Care Unit Patients After Surgery

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OBJECTIVES. To examine the relative proportions of central line–associated bloodstream infection (BSI) due to gram-negative bacteria and due to gram-positive bacteria among patients who had undergone surgery and patients who had not. The study also evaluated clinical predictive factors and unadjusted outcomes associated with central line–associated BSI caused by gram-negative bacteria in the postoperative period.

DESIGN. Observational, case-control study based on a retrospective review of medical records.

SETTING. University of Chicago Medical Center, a 500-bed tertiary care center located on Chicago’s south side.

PATIENTS. Adult intensive care unit (ICU) patients who developed central line–associated BSI.

RESULTS. There were a total of 142 adult patients who met the Centers for Disease Control and Prevention National Nosocomial Infection Surveillance System definition for central line–associated BSI. Of those, 66 patients (46.5%) had infections due to gram-positive bacteria, 49 patients (34.5%) had infections due to gram-negative bacteria, 23 patients (16.2%) had infections due to yeast, and 4 patients (2.8%) had mixed infections. Patients who underwent surgery were more likely to develop central line–associated BSI due to gram-negative bacteria within 28 days of the surgery, compared with patients who had not had surgery recently (57.6% vs 27.3%; \( P = .002 \)). On multivariable logistic regression analysis, diabetes mellitus (adjusted odds ratio [OR], 4.6 [95% CI, 1.2-18.1]; \( P = .03 \)) and the presence of hypotension at the time of the first blood culture positive for a pathogen (adjusted OR, 9.8 [95% CI, 2.5-39.1]; \( P = .001 \)) were found to be independently predictive of central line–associated BSI caused by gram-negative bacteria. Unadjusted outcomes were not different in the group with BSI due to gram-negative pathogens, compared to the group with BSI due to gram-positive pathogens.

CONCLUSIONS. Clinicians caring for critically ill patients after surgery should be especially concerned about the possibility of central line–associated BSI caused by gram-negative pathogens. The presence of diabetes and hypotension appear to be significant associated factors.

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The proportion of healthcare-associated bloodstream infection (BSI) caused by gram-negative organisms has been found to be increasing in recent decades.¹ BSI caused by gram-negative pathogens in hospitalized patients is associated with greater morbidity and higher mortality, compared with BSI caused by gram-positive bacteria.² Infections caused by *Pseudomonas aeruginosa* have been associated with particularly poor outcomes.³

Among patients in surgical intensive care units (ICUs), central line-associated BSI has been shown to be associated with increased resource use, including an average 20-day increase in ICU length of stay and an excess hospital cost of $56,167 per patient, compared with the stays and costs for patients who did not develop central line–associated BSI.⁴ In another study of surgical ICU patients, gram-negative bacteria caused 37% of BSIs, although gram-positive bacteria, particularly staphylococci and enterococci, remained the most common cause of BSI.⁵ Previous studies examining cardiac and oncologic surgery patients found that postoperative BSI in these populations is more commonly caused by gram-negative pathogens than gram-positive pathogens.⁶⁻⁷ However, these studies did not specifically examine clinical predictors of central line–associated BSI due to gram-negative pathogens. As a result, clinicians have little guidance as to whether the empirical antimicrobial regimen for suspected central line–associated BSI in a patient who has undergone surgery should include antimicrobials active against gram-negative pathogens. We hypothesized that not only are gram-negative
bacteria more commonly associated with central line–associated BSI in patients who have undergone surgery, but that there may be specific factors that are predictive of central line–associated BSI due to gram-negative pathogens among this group of patients. Given a high proportion of infections caused by gram-negative pathogens, the identification of reliable clinical predictors of gram-negative pathogens, as opposed to gram-positive pathogens, as the cause of central line–associated BSI could help clinicians select appropriate antimicrobial regimens when caring for a patient in the surgical ICU with suspected central line–associated BSI.

The present study was conducted to evaluate the relative proportions of central line–associated BSI due to gram-negative bacteria and due to gram-positive bacteria among ICU patients who underwent surgery, compared with ICU patients who did not undergo surgery. Further, we evaluated specific clinical predictors for the development of central line–associated BSI caused by gram-negative bacteria in ICU patients who underwent surgery. Finally, as a secondary objective, the crude outcomes associated with BSI caused by gram-negative bacteria were compared with the outcomes associated with BSI due to gram-positive pathogens.

**Methods**

**Study Population and Setting**

The study population was drawn from adult inpatients in the ICUs at the University of Chicago Medical Center, a 500-bed tertiary care center located on Chicago’s south side that serves a diverse patient population, including a large proportion of African American patients. In addition to routine medical and surgical services, the hospital offers highly specialized care, including solid-organ and bone marrow transplantation. There are 6 ICUs for adult patients (medical, cardiac surgery, cardiology, neurosurgery, general surgery, and burn ICUs), with a total capacity of more than 60 inpatients.

The study included patients hospitalized in any of these 6 ICUs during the period from August 2002 through May 2005. Patients were identified from central line–associated BSI surveillance data routinely collected by the hospital’s infection control program. Criteria established by the Centers for Disease Control and Prevention (CDC) for the National Nosocomial Infections Surveillance (NNIS) System were used to define central line–associated BSI, no matter the causative organism. Central line–associated BSI due to potential skin contaminants (including coagulase-negative staphylococci) were defined in accordance with the CDC definition.

Blood cultures were performed for adult patients in accordance with recommended procedures, by use of a blood culture system (Bectec 9240 Blood Culture System; Becton Dickinson Diagnostics) and a variety of culture vials (Bectec Standard/10 Aerobic/F Medium for patients who did not receive antibiotic therapy, Bactec Plus Aerobic/F Medium for patients who did receive antibiotic therapy; or Bectec Standard Aerobic/F Medium; all manufactured by Becton Dickinson Diagnostics). The distribution of central line–associated BSIs caused by specific pathogens was examined to exclude the occurrence of any clusters or outbreaks of infections due to a single organism during the study period. Throughout the study period, the protocol for central line insertion included placement after appropriate hand hygiene with antimicrobial soap and water, the use of maximal sterile barrier precautions, and the use of a subclavian site for catheter placement whenever feasible. Infection control practices were uniform across the various ICUs.

**Study Design**

An observational study based on a retrospective review of patient medical records, clinical microbiology results, and infection control records was conducted. In the first phase of the study, the records of ICU patients identified by routine infection control surveillance as having central line–associated BSI were reviewed to identify the patients who underwent surgery within the 4 weeks prior to the onset of BSI. Surgery was defined as an operative procedure performed within 28 days before the first blood culture positive for a pathogen and performed during the same hospitalization in which the patient developed BSI. Invasive procedures performed outside the operating room were excluded. The proportion of BSIs caused by gram-negative bacteria and the proportion caused by gram-positive bacteria were compared for patients with and without a history of surgery.

In the second phase of the study, we used a case-control design to examine predictive factors potentially associated with the development of central line–associated BSI due to gram-negative bacteria in ICU patients who underwent surgery. Case patients were defined as ICU patients who underwent surgery and developed central line–associated BSI caused by gram-negative bacteria. Control patients were defined as ICU patients who underwent surgery and subsequently developed central line–associated BSI due to gram-positive bacteria. Clinical data abstraction was done from patients’ paper and electronic medical records. One abstractor performed the review of all records.

We evaluated the following candidate predictors of central line–associated BSI: (1) factors related to surgery (the number of surgical procedures performed within 28 days prior to the onset of central line–associated BSI, the number of days from the preceding surgery to the onset of central line–associated BSI, whether the surgery was emergent or nonemergent, type of surgical procedure, and American Society of Anesthesiologists score [ie, a score of 4 or greater vs a score of less than 4]), (2) factors related to the catheter(s) (anatomic site, number of lumens, number of catheters, whether placement was emergent or nonemergent, and number of catheter-days prior to onset of BSI), (3) receipt of antimicrobial therapy, (4) receipt of immunosuppressive therapy (by class), (5) age,
RESULTS

A total of 142 episodes of central line–associated BSI occurred after 55,389 catheter-days of central line use; the overall rate of catheter-associated BSI among adult ICU patients during the study period was 2.56 infections per 1,000 catheter-days. Of those infections, 66 (46.5%) were due to gram-positive bacteria, 49 (34.5%) were due to gram-negative bacteria, 23 (16.2%) were due to yeast, and 4 (2.8%) were caused by a mix of gram-negative and gram-positive organisms. There were 115 episodes of central line–associated BSI due to either gram-positive or gram-negative organisms among 114 patients (2 episodes due to gram-positive pathogens occurred in the same patient.) Of these patients, 59 underwent surgery within 28 days prior to the onset of central line–associated BSI, and 55 did not. The causative organism was gram-negative in 34 (57.6%) of the 59 patients who underwent surgery and in 15 (27.3%) of the 55 patients who did not undergo surgery. This difference between the 2 groups was statistically significant (unadjusted OR, 3.6 [95% CI, 1.7–8.0]; \( P = .002 \)).

Of the 59 ICU patients who underwent surgery and developed BSI due to a gram-negative organism or a gram-positive organism, 57 were included in the analysis of predictive factors (33 case patients and 24 control patients). One patient in the gram-negative pathogen group and 1 patient with BSI in the gram-positive pathogen group had incomplete medical records and were excluded. A variety of pathogens were found in the 33 patients in the gram-negative pathogen group, including Enterobacter species (10 isolates [30%]), Klebsiella species (8 [24%]), Citrobacter freundii (4 [12%]), Pseudomonas aeruginosa (4 [12%]), Acinetobacter baumanii (2 [6%]), Serratia marcescens (2 [6%]), and other (3 [9%]). The isolates recovered from the 24 patients in the gram-positive pathogen group were coagulase-negative Staphylococcus (12 isolates [50%]), Enterococcus faecalis (6 [25%]), Enterococcus faecium (4 [18%]), and Staphylococcus aureus (2 [7%]).

The 57 patients in the case-control study underwent a total of 96 surgical procedures within the 28 days prior to the onset of central line–associated BSI. The types of surgery were as follows: cardiac (28 procedures [29.2%]), plastic or reconstructive (28 [29.2%]), neurologic (14 [14.6%]), vascular (9 [9.4%]), thoracic (7 [7.3%]), liver or kidney transplantation (4 [4.2%]), and other surgery (6 [6.2%]). The median duration of catheter use was 13 days among patients in the gram-negative pathogen group and 10.5 days among patients in the gram-positive pathogen group (\( P > .05 \)). The median duration from the earliest surgery to the day of the first bloodstream culture positive for a pathogen was 5 days for patients in the gram-negative pathogen group and 5.5 days for patients in the gram-positive pathogen group. A total of 100 central venous catheters were present in these 57 patients at the onset of BSI; 6 were inserted through peripheral veins, 24 were
Table 1. Factors Associated With Central Line–Associated Bloodstream Infection (CL-BSI) in Intensive Care Unit Patients Who Underwent Surgery, on Univariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>With CL-BSI due to GNB (n = 33)</th>
<th>With CL-BSI due to GPB (n = 24)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension at time of first blood culture positive for a pathogen</td>
<td>20 (60.6)</td>
<td>3 (13.0)</td>
<td>10.8 (2.7-43.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Presence of a catheter at onset of CL-BSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-lumen catheter</td>
<td>16 (48.5)</td>
<td>4 (16.7)</td>
<td>4.7 (1.3-16.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Femoral catheter</td>
<td>13 (39.4)</td>
<td>3 (12.5)</td>
<td>4.6 (1.1-18.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Vasopressive therapy in the 24 hours before onset of CL-BSI</td>
<td>11 (36.7)</td>
<td>2 (9.5)</td>
<td>5.5 (1.1-27.7)</td>
<td>.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (45.0)</td>
<td>5 (20.8)</td>
<td>3.2 (1.0-10.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Cefazolin therapy on the day of surgery</td>
<td>8 (24.0)</td>
<td>1 (4.2)</td>
<td>7.4 (0.9-63.5)</td>
<td>.06</td>
</tr>
<tr>
<td>Outpatient corticosteroid therapy</td>
<td>8 (24.0)</td>
<td>1 (4.2)</td>
<td>7.4 (0.9-63.5)</td>
<td>.06</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16 (48.5)</td>
<td>6 (25.0)</td>
<td>2.8 (0.9-8.9)</td>
<td>.07</td>
</tr>
<tr>
<td>Extended-spectrum cephalosporin therapy prior to the day of surgery</td>
<td>4 (12.0)</td>
<td>8 (33.0)</td>
<td>0.3 (0.1-1.1)</td>
<td>.1</td>
</tr>
</tbody>
</table>

Note. CI, confidence interval; GNB, gram-negative bacteria; GPB, gram-positive bacteria; OR, odds ratio.

Table 2. Predictive Factors for Central Line–Associated Bloodstream Infection due to Gram-Negative Bacteria on Multivariable Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted OR</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension at time of first blood culture positive for a pathogen</td>
<td>10.8</td>
<td>9.8 (2.5-39.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.2</td>
<td>4.6 (1.2-18.1)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Note. CI, confidence interval; OR, odds ratio.
line–associated BSI. Because postoperative infections caused by gram-negative pathogens are most commonly anticipated for patients who undergo surgeries involving gastrointestinal transection, it is particularly interesting that in this study, 49 (86%) of the 57 patients who had surgery during the 4 weeks prior to the onset of BSI underwent procedures that did not involve the abdomen.

Although the explanation for the increased frequency with which gram-negative bacteria cause BSI among surgical patients remains uncertain, it is possible that the infections that occur during the postoperative period are more likely to be caused by gram-negative bacilli as a result of selection pressure, because perioperative antimicrobial prophylaxis is mainly targeted towards gram-positive pathogens. Perioperative antibiotic prophylaxis has been shown to modify the colonization profile of the patient.\(^{12-16}\) The results of this study demonstrated a trend toward development of BSI due to gram-negative bacteria among patients who were exposed to cefazolin on the day of surgery. However, exposure to vancomycin before, during, or after the surgery did not favor the development of BSI due to gram-negative organisms. Further study is needed to definitively determine the influence of perioperative antibiotic prophylaxis on the development of BSI due to gram-negative pathogens among patients who have undergone surgery. It also remains to be determined how factors other than the antibiotic therapy associated with surgery, such as exposure to anesthesia and perioperative care, might predispose a patient to develop BSI due to gram-negative pathogens.

Although the present study was not designed to compare the risk of infection for ICU patients who underwent surgery and ICU patients who did not, the results shed light on certain factors that appear to be predictive of the development of BSI due to gram-negative or gram-positive organisms in ICU patients after recent surgery. The findings of the present study provide valuable information to clinicians selecting empirical antimicrobial therapy for patients with suspected BSI during the postoperative period. By use of multivariable regression analysis, this study found that diabetes mellitus is independently associated with BSI due to gram-negative bacteria in patients who underwent surgery. This finding is consistent with the results of previous published reports. Diabetes is a known risk factor for bacteremia due to gram-negative bacteria such as Enterobacter species\(^ {17}\) and extended-spectrum \(\beta\)-lactamase–producing Klebsiella pneumoniae.\(^ {18}\) People with diabetes are also more likely to be colonized with gram-negative organisms, compared with people who do not have diabetes.\(^ {19}\) Ryan et al.\(^ {6}\) showed that BSI in the early postoperative period after cardiac surgery was more likely to be caused by gram-negative bacteria than by gram-positive bacteria and that diabetes is a risk factor for the development of any postoperative bacteremia. When central line–associated BSI is suspected in an ICU patient who has undergone surgery, the presence of diabetes favors gram-negative bacteria as opposed to gram-positive pathogens as the cause of the infection, and it is important to choose empirical antibiotics with reliable activity against gram-negative organisms.

The present study also found that among ICU patients who underwent surgery, the presence of hypotension at the onset of BSI was significantly associated with an infection in which gram-negative bacteria are the primary etiologic agent. Studies done in the 1960s and 1970s showed that hypotension is more common if bacteremia is caused by gram-negative organisms, compared with gram-positive organisms.\(^ {20-23}\) The results of this study reaffirm this finding in the population of patients who develop central line–associated BSI after surgery. Importantly, in this study the majority of the central line–associated BSI due to gram-positive organisms was caused by coagulase-negative staphylococci, which are known not to be very virulent, except for certain species such as Staphylococcus lugdunensis.\(^ {24,25}\) As a result, patients infected with gram-positive bacteria in this study may not have appeared as acutely ill as the patients infected with more-virulent gram-negative pathogens, exaggerating the association between hypotension and these organisms.

The results of the current study should be confirmed in a larger population of patients, but the findings still serve as an important reminder to clinicians caring for critically ill patients after surgery. Although gram-positive bacteria, such as staphylococci, must be considered as causative organisms for infections in patients with suspected central line–associated BSI, it is especially critical to consider empirical antimicrobial therapy that is active against gram-negative pathogens as well, particularly if the patient has diabetes, has hypotension, and/or has recently undergone surgery.

The risk factor analysis described here has several limitations, which include a small data set from a single institution with limited statistical power, as well as potential unmeasured and unknown confounding factors. The retrospective nature of the study, which was based on the review of medical records, is also a limitation. Future studies on the development of a predictive model for the etiology of central line–associated BSI should include a larger patient population in varied settings, to allow for validation of specific predictive rules.

The present study did not find a significant difference in crude mortality, length of hospital stay, or length of ICU stay for ICU patients who underwent surgery and subsequently developed central line–associated BSI due to gram-negative organisms, compared with those who developed BSI due to gram-positive organisms. That no difference was detected in the present study, even considering the high proportion of infections due to gram-positive organisms that were caused by less-virulent coagulase-negative staphylococci, is surprising. The outcomes in this study were not adjusted for important variables, such as severity of illness, receipt of adequate antimicrobial therapy, or catheter removal, and therefore, their significance is limited. These results will need to be confirmed in a larger study that is defined to account for the confounding associated with these other factors.

Clinicians caring for critically ill patients who have un-
dergone surgery need to be especially concerned about the possibility of central line–associated BSI due to gram-negative pathogens. Vigilance should be especially intense when the clinician is confronted with a patient who has diabetes or who is hemodynamically unstable.

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