Development of Institutional Guidelines for Management of Gram-Negative Bloodstream Infections: Incorporating Local Evidence

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Abstract

Background: Appropriate empirical antimicrobial therapy is associated with improved outcomes of patients with Gram-negative bloodstream infections (BSI). **Objective:** Development of evidence-based institutional management guidelines for empirical antimicrobial therapy of Gram-negative BSI. **Methods:** Hospitalized adults with Gram-negative BSI in 2011–2012 at Palmetto Health hospitals in Columbia, SC, USA, were identified. Logistic regression was used to examine the association between site of infection acquisition and BSI due to *Pseudomonas aeruginosa* or chromosomally mediated AmpC-producing *Enterobacteriaceae* (CAE). Antimicrobial susceptibility rates of bloodstream isolates were stratified by site of acquisition and acute severity of illness. Retained antimicrobial regimens had predefined susceptibility rates $\geq 90\%$ for noncritically ill and $\geq 95\%$ for critically ill patients. **Results:** Among 390 patients, health care-associated (odds ratio [OR]: 3.0, 95% confidence interval [CI]: 1.5–6.3) and hospital-acquired sites of acquisition (OR: 3.7, 95% CI: 1.6–8.4) were identified as risk factors for BSI due to *P. aeruginosa* or CAE, compared with community-acquired BSI (referent). Based on stratified bloodstream antibiogram, ceftriaxone met predefined susceptibility criteria for community-acquired BSI in noncritically ill patients (95%). Cefepime and piperacillin-tazobactam monotherapy achieved predefined susceptibility criteria in noncritically ill (95% both) and critically ill patients with health care-associated and hospital-acquired BSI (96% and 97%, respectively) and critically ill patients with community-acquired BSI (100% both). **Conclusions:** Incorporation of site of acquisition, local antimicrobial susceptibility rates, and acute severity of illness into institutional guidelines provides objective evidence-based approach for optimizing empirical antimicrobial therapy for Gram-negative BSI. The suggested methodology provides a framework for guideline development in other institutions.

Keywords

bacteremia, sepsis, antibiotics, *Escherichia coli*, *Enterobacter cloacae*

Introduction

Bloodstream infections (BSI) have a significant impact on the morbidity and mortality in the general population as nearly 500 000 individuals develop BSI annually in the United States, contributing to 75 000 deaths.¹ Adequate antimicrobial therapy is a key factor in reducing the burden of BSI, as inadequate antimicrobial therapy has been associated with increased mortality, cost, and length of stay in the hospital.^{2–5} Despite the extensive use of broad-spectrum antimicrobial agents, it is alarming that 15% to 30% of patients with BSI still receive inadequate empirical therapy.^{6,7}

The initial selection of the empirical antimicrobial regimen in patients with Gram-negative BSI is a difficult task due to lack of knowledge of the identification of the bloodstream isolate and in vitro antimicrobial susceptibility results within

72 hours of presentation. Therefore, the development of local guidelines for management of BSI may be an effective tool to improve empirical antimicrobial therapy and hence patient outcomes.¹

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Antimicrobial stewardship programs play an important role in the development of institutional management guidelines in hospitalized patients with serious infections.⁸ Modification of national guidelines to tailor to the specific characteristics of an institution is an important step in development of local guidelines. However, lack of national guidelines for management of Gram-negative BSI emphasizes the need for antimicrobial stewardship programs to develop institutional management recommendations to guide empirical antimicrobial therapy based on local data. The aim of the study was to develop institutional guidelines for empirical antimicrobial therapy of Gram-negative BSI based on site of infection acquisition, local bloodstream antibiogram, and acute severity of illness.

Methods

Setting

The study was conducted at Palmetto Health Richland and Baptist hospitals in Columbia, SC, USA. The two hospitals predominantly serve the population of Richland County and surrounding counties in central South Carolina. Restricted antimicrobial agents with Gram-negative activity at both hospital formularies at the time of study included carbapenems, ceftazoline, and tigecycline. The Institutional Review Board of the two hospitals approved the study and waived informed consent.

Definitions

Gram-negative BSI was defined as the growth of any aerobic Gram-negative bacillus in a blood culture. The source of BSI was defined according to the Centers for Disease Control and Prevention (CDC) criteria.⁹ The site of infection acquisition was classified into community-acquired, health care-associated, and hospital-acquired as previously defined.¹⁰ Adequacy of empirical antimicrobial therapy was defined based on dosing, route of administration, and in vitro antimicrobial susceptibility testing as previously defined.³ Briefly, empirical antimicrobial therapy was considered adequate if (1) bloodstream isolate was susceptible to empirical agent based on in vitro antimicrobial susceptibility results using Clinical and Laboratory Standards Institute (CLSI) criteria; (2) empirical antimicrobial agent was administered intravenously, with the exception of fluoroquinolones which were considered appropriate if administered orally in hemodynamically stable patients due to high bioavailability; and (3) patient received at least the minimum recommended dose of an antimicrobial agent according to the medication package insert for creatinine clearance at the time of BSI.

Case Ascertainment

All patients with BSI due to aerobic Gram-negative bacilli from January 1, 2011, to December 31, 2012, were identified

through microbiology laboratory databases. Hospitalized adult patients with first episodes of monomicrobial Gram-negative BSI were included in the study ($n = 390$). Patients <18 years old ($n = 62$), polymicrobial BSI ($n = 79$), recurrent episodes of BSI ($n = 24$), and patients who were treated outside the hospital ($n = 23$) were excluded.

Guideline Development and Assessment

Hospital-acquired and health care-associated sites of acquisition have been previously identified as risk factors for BSI due to Gram-negative bacilli that inherently harbor antimicrobial resistance genes such as *Pseudomonas aeruginosa* and chromosomally mediated AmpC-producing *Enterobacteriaceae* (CAE), including *Enterobacter*, *Citrobacter*, and *Serratia* species.^{11,12} The first step in guideline development was to confirm this finding in the local setting using a retrospective case-control design. Second, in vitro antimicrobial susceptibility rates of bloodstream isolates for various antimicrobial agents and combinations regimens were examined in each site of acquisition. Antimicrobial agents with $\geq 90\%$ in vitro susceptibility rates were retained. Third, patients were stratified by acute severity of illness using the Pitt bacteremia score.¹³ Antimicrobial regimens were retained if susceptibility rates were $\geq 90\%$ for noncritically ill patients (Pitt bacteremia score <4) and $\geq 95\%$ for critically ill patients (Pitt bacteremia score ≥ 4). Minimum susceptibilities of 90% and 95% for recommended antimicrobial regimens in noncritically ill and critically ill patients, respectively, represented the 90th percentile of responses to a large survey that was conducted among antimicrobial stewardship pharmacists.¹⁴ The preference for selection into institutional guidelines was given for monotherapy of nonrestricted agents. If monotherapy of all nonrestricted agents did not meet predefined susceptibility criteria in any category, restricted antimicrobial agents and combination regimens were included for selection in the respective category.

After management guidelines were developed, potential to improve the adequacy of empirical antimicrobial therapy and impact on utilization of broad-spectrum antibiotics was evaluated. First, the adequacy of empirical antimicrobial therapy for Gram-negative BSI in the historic cohort was compared with projected adequacy if the guidelines were fully implemented. Second, the proportion of patients who received empirical antipseudomonal agents in the historic cohort was compared with projected use after guidelines implementation.

Statistical Analysis

Logistic regression was used to examine impact of site of infection acquisition on risk of BSI due to *P. aeruginosa* or CAE. Demographics and clinical variables were collected from electronic medical records in patients with BSI due to *P. aeruginosa* or CAE (cases) and other Gram-negative bacilli

Table 1. Demographics and Clinical Characteristics of Patients With Gram-Negative Bloodstream Infections.

Variable	(n = 390)
Age, median (IQR)	66 (55-78)
Female sex	229 (59)
Ethnicity	
White	191 (49)
African American	188 (48)
Other	11 (3)
Diabetes mellitus	144 (37)
End-stage renal disease	38 (10)
Liver cirrhosis	6 (2)
Malignancy	70 (18)
Site of acquisition	
Community-acquired	161 (41)
Health care-associated	159 (41)
Hospital-acquired	70 (18)
Source of infection	
Urinary tract	216 (55)
Gastrointestinal tract	50 (13)
Central venous catheter	35 (9)
Skin and soft tissue	17 (4)
Respiratory tract	12 (3)
Other	8 (2)
Unknown	52 (13)

Note. Data are shown as number (%) unless otherwise specified.
IQR = interquartile range.

(controls), including age, sex, ethnicity, chronic comorbidities, and site of infection acquisition.

JMP (version 11.0, SAS Institute Inc, Cary, North Carolina) was used for statistical analysis. The level of significance for statistical testing was defined as $P < .05$ (2-sided).

Results

Over the 2-year study period, 390 patients with Gram-negative BSI were included from the 2 hospitals. Overall, the median age was 66 years, 229 (59%) were women, and the urinary tract (216; 55%) was the most common source of infection. The majority of patients had either community-acquired (161; 41%) or health care-associated BSI (159; 41%), whereas the remaining 70 patients (18%) had hospital-acquired infections (Table 1).

Escherichia coli was predominantly the most common bloodstream isolate among community-acquired and health care-associated BSI accounting for two-thirds and one-half of cases, respectively (Table 2). It represented one-third of hospital-acquired bloodstream isolates, ranking second just behind *Klebsiella* species. Combined, *P. aeruginosa* and CAE were more common in hospital-acquired (16; 23%) and health care-associated (31; 19%) than in community-acquired BSI (12; 7%). The site of infection acquisition

Table 2. Microbiology of Gram-Negative Bloodstream Infections by Site of Acquisition.

Bacteria	Community-acquired (n = 161)	Health care-associated (n = 159)	Hospital-acquired (n = 70)
<i>Escherichia coli</i>	106 (66)	79 (50)	22 (31)
<i>Klebsiella</i> species	24 (15)	27 (17)	26 (37)
<i>Proteus mirabilis</i>	12 (7)	16 (10)	3 (4)
<i>Pseudomonas aeruginosa</i>	4 (2)	10 (6)	6 (9)
<i>Enterobacter</i> species	4 (2)	10 (6)	5 (7)
<i>Serratia</i> species	1 (1)	8 (5)	4 (6)
<i>Citrobacter</i> species	3 (2)	3 (2)	1 (1)
Other	7 (4)	6 (4)	3 (4)

Note. Data are shown as number (%).

Table 3. Risk Factors of Bloodstream Infections Due to *Pseudomonas aeruginosa* or Chromosomally Mediated AmpC-Producing *Enterobacteriaceae*.

Risk factor	Odds ratio	95% CI	P value
Age (per decade)	0.96	(0.82-1.31)	.64
Male sex	1.34	(0.77-2.35)	.30
White ethnicity	0.93	(0.53-1.62)	.80
Diabetes mellitus	0.86	(0.47-1.52)	.60
Liver cirrhosis	1.12	(0.06-7.14)	.92
Cancer	1.36	(0.67-2.62)	.38
Indwelling urinary catheter	1.45	(0.52-3.50)	.44
Site of acquisition			
Community-acquired		Referent	
Health care-associated	3.01	(1.52-6.32)	.001
Hospital-acquired	3.68	(1.64-8.44)	.002

Note. CI = confidence interval.

identified patients at risk of BSI due to *P. aeruginosa* or CAE. Patients with health care-associated and hospital-acquired BSI were nearly 3 times more likely to have BSI due to *P. aeruginosa* or CAE as compared with those with community-acquired BSI (Table 3).

In vitro antimicrobial susceptibilities of Gram-negative bloodstream isolates to various antimicrobial agents and combination regimens by site of infection acquisition are demonstrated in Table 4. Ceftriaxone was the only nonrestricted nonantipseudomonal agent that provided $\geq 90\%$ in vitro antimicrobial susceptibility for community-acquired Gram-negative bloodstream isolates. Three nonrestricted antipseudomonal agents, including two beta-lactams (cefepime and piperacillin-tazobactam) and gentamicin, had $\geq 90\%$ susceptibility against both health care-associated and hospital-acquired Gram-negative bloodstream isolates. Because there was marginal difference between in vitro antimicrobial susceptibility rates of health care-associated and hospital-acquired Gram-negative bloodstream isolates, the two groups were merged together.

Table 4. In Vitro Antimicrobial Susceptibility of Bloodstream Isolates by Site of Acquisition.

Antimicrobial agent/combination	Community-acquired (n = 161)	Health care– associated (n = 159)	Hospital-acquired (n = 70)
Ampicillin	63 (39)	47 (30)	17 (24)
Ampicillin-sulbactam	112/160 (70)	99/158 (63)	46 (66)
Cefazolin	128/160 (80)	112 (70)	47 (67)
Ceftriaxone	151 (94)	139 (87)	58/69 (84)
Cefepime	156 (97)	152 (96)	66 (96)
Piperacillin-tazobactam	157/159 (99)	151/157 (96)	65/69 (94)
Ertapenem	157 (98)	149 (94)	64 (91)
Meropenem	161 (100)	158 (99)	68 (97)
Ciprofloxacin	134 (83)	123/158 (78)	60/68 (88)
Gentamicin	147/158 (93)	148/158 (94)	63/69 (91)
Trimethoprim-sulfamethoxazole	126/160 (79)	119/159 (75)	53 (76)
Cefepime + gentamicin	157 (98)	155/159 (97)	67/69 (97)
Cefepime + ciprofloxacin	158 (98)	152 (96)	66/69 (96)
Piperacillin-tazobactam + gentamicin	159 (99)	155/158 (98)	67 (96)
Piperacillin-tazobactam + ciprofloxacin	159/160 (99)	152/158 (96)	66/69 (96)
Meropenem + gentamicin	161 (100)	159 (100)	69 (99)
Meropenem + ciprofloxacin	161 (100)	158 (99)	69/69 (100)

Note. Data show number of susceptible isolates (%) or number of susceptible/number of tested isolates (%), if not all isolates were tested.

Table 5. In Vitro Antimicrobial Susceptibility of Bloodstream Isolates by Site of Acquisition and Acute Severity of Illness.

Antibiotic	Community-acquired		Health care–associated or hospital-acquired	
	Pitt score <4 (n = 128)	Pitt score ≥4 (n = 33)	Pitt score <4 (n = 152)	Pitt score ≥4 (n = 77)
Ceftriaxone	121 (95)	30 (91)	NA	NA
Cefepime	123 (96)	33 (100)	144 (95)	74 (96)
Piperacillin-tazobactam	124/126 (98)	33 (100)	143/151 (95)	73/75 (97)
Gentamicin	115/126 (91)	32 (97)	142/151 (94)	69/76 (91)

Note. Data show number of susceptible isolates (%) or number of susceptible/number of tested isolates (%), if not all isolates were tested. NA = not appropriate.

Next, patients were stratified based on site of acquisition (community-acquired vs health care–associated/hospital-acquired) and acute severity of illness using the Pitt bacteremia score (Table 5). Utilizing stratified bloodstream antibiogram, ceftriaxone was selected for community-acquired BSI in noncritically ill patients based on narrower spectrum of activity compared with the remaining nonrestricted agents. Cefepime and piperacillin-tazobactam were the only nonrestricted agents that met predefined criteria in critically ill patients with health care–associated/hospital-acquired BSI. The two antipseudomonal beta-lactams were selected over gentamicin in the remaining categories based on preferable side effects profile. An algorithm was developed to guide empirical antimicrobial therapy in patients with Gram-negative BSI while awaiting final blood culture results (Figure 1).

In the current cohort, 92% of patients received adequate empirical antimicrobial therapy for Gram-negative BSI and

82% received at least one antipseudomonal agent empirically. Implementation of proposed guidelines is projected to increase adequacy of empirical antimicrobial therapy to over 95% and reduce utilization of empirical antipseudomonal agents to 67% (262/390) of patients.

Discussion

Improvement in quality of care and reduction in antimicrobial resistance rates are 2 major principles of antimicrobial stewardship.¹⁵ Institutional guidelines for management of hospitalized patients with serious infections are essential tools to improve quality of care by optimization of empirical antimicrobial therapy. In addition, if these guidelines advocate for reduction in utilization of broad-spectrum antimicrobial regimens, then implementation may contribute to reduction in antimicrobial resistance rates as well.⁸ This article outlines suggested methodology for development of

Figure 1. Guidelines for empirical antimicrobial therapy of gram-negative bloodstream infections.

Note. BSI = bloodstream infection; IV = intravenous.

evidence-based institutional guidelines for management of Gram-negative BSI utilizing local data, which may provide framework for other institutions.

It is important for institutional management guidelines to represent high-quality evidence-based data. At the same time, guidelines that are practical and user friendly are more likely to be accepted and implemented across the institution. For this reason, many institutional management guidelines are centered midway between science and practice, and the current guidelines are an example of this role. The study did not aim to develop a model to predict BSI due to resistant Gram-negative bacilli. That would have required inclusion of many additional clinical variables and detailed history of prior antibiotic use in each patient.^{16,17} Rather, the goal of this study was to develop institutional guidelines for empirical therapy of Gram-negative BSI using clinical criteria that most health care providers were familiar with regardless of specialty, such as site of infection acquisition and acute severity of illness. The Pitt bacteremia score was used as a measure of acute severity of illness to maintain consistent definition of critically ill throughout guideline development. Health care providers were encouraged to use objective methods to determine acute severity of illness and prognosis of patients with BSI.^{13,18} However, the definition of critically ill was expanded to include patients who required admission to the intensive care unit to make the guidelines more practical for health care providers who were not familiar with such scores (Supplement 1).

Using antimicrobial agents with $\geq 90\%$ susceptibility in noncritically ill patients with BSI is consistent with national guidelines for management of acute pyelonephritis and nosocomial pneumonia.^{19,20} However, the predefined minimum susceptibility threshold of $\geq 95\%$ for critically ill patients in this study may seem optimistic in areas with high rates of antimicrobial resistance. These cutoffs were derived from a large national survey of antimicrobial stewardship pharmacists who have knowledge of antimicrobial resistance rates and local hospital epidemiology.¹⁴ It was conceivable to

select higher minimum antimicrobial susceptibility cutoff in critically ill patients because survival benefit from adequate empirical antimicrobial therapy was clearly demonstrated in this population.³ However, these cutoffs remain subject for revision at the discretion of local antimicrobial stewardship programs.

Despite relatively high overall susceptibility rates of bloodstream isolates to beta-lactams in the current study, susceptibility to ampicillin-sulbactam did not exceed 70% even in community-acquired bloodstream isolates. Similarly, ciprofloxacin did not meet the predefined susceptibility selection criteria in any category. This is consistent with data from other population-based settings in the USA.²¹ The predefined minimum susceptibility thresholds in this study were achieved by ceftriaxone in noncritically ill patients with community-acquired BSI and either piperacillin-tazobactam or cefepime in critically ill patients with community-acquired BSI and those with health care-associated or hospital-acquired BSI. The relatively low incidence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* among the local bloodstream isolates likely allowed the use of carbapenem-sparing regimens as first line treatment options. Overall, 3.3% (13/390) of Gram-negative bacilli in this study demonstrated ESBL production (3.1% [4/128] in noncritically ill, community-acquired group and 3.4% [9/262] in the other stratum of the guidelines). Moreover, it was noted in the current study that adding a fluoroquinolone or an aminoglycoside to beta-lactams provided minimal improvement in antimicrobial susceptibility rates, regardless of site of acquisition. This argued against the nonstratified use of combination antimicrobial therapy for Gram-negative BSI in our local population.

It was projected that implementation of the current management guidelines would improve the adequacy of empirical antimicrobial therapy to $>95\%$. Multiple measures were taken to improve the adequacy of antimicrobial therapy in the remaining patients. Providers were highly encouraged to contact the antimicrobial stewardship and support team or request an infectious diseases consultation for more specific

recommendations on empirical antimicrobial therapy in patients with unique clinical situations such as severe beta-lactam allergy or in the case of suspicion of a particular antimicrobial resistance mechanism, including ESBL production, as in Supplement 1.²²⁻²⁵ Moreover, the antimicrobial stewardship and support team would prospectively follow every patient to ensure proper implementation of guidelines and provide additional recommendations in patients with risk factors for antimicrobial resistance.

Guideline implementation is also projected to reduce overall utilization of antipseudomonal agents. Prospective monitoring by the antimicrobial stewardship and support team to ensure appropriate de-escalation of antimicrobial regimen based on bacterial identification and in vitro antimicrobial susceptibility testing results may also shorten the duration of antipseudomonal therapy. Because the guidelines provide reassurance to health care providers that monotherapy adequately covers $\geq 95\%$ of bloodstream isolates, it is expected that use of combination antimicrobial therapy may also decline after implementation.

The current guidelines have limitations that may impact implementation at other institutions. First, accurately defining the site of infection acquisition may be challenging in patients with unknown or limited medical histories within the local health care system. Second, because all recommended regimens constitute beta-lactam antibiotics, mechanisms to screen patients and recommend alternative therapy in those with severe beta-lactam allergy are necessary. Finally, there are potential risks of not providing initial adequate coverage for *P. aeruginosa* in noncritically ill patients with community-acquired BSI and ESBL-producing *Enterobacteriaceae* overall, particularly in settings with higher incidence of BSI due to these resistant bacteria than the current population. The use of more robust models to predict the risk of BSI due to *P. aeruginosa* and ESBL-producing *Enterobacteriaceae* has been demonstrated to improve both the adequacy of empirical therapy and antimicrobial utilization.^{16,26}

In summary, the study provides suggested methods for development of institutional management guidelines for Gram-negative BSI based on site of acquisition, local antimicrobial susceptibility rates of bloodstream isolates, and acute severity of illness. Implementation of these institutional guidelines may improve the adequacy of empirical antimicrobial therapy for Gram-negative BSI while reducing utilization of broad-spectrum antimicrobial agents.

Authors' Note

The preliminary results of this study were presented in part at IDWeek; October 2014; Philadelphia, PA, USA (Abstract No. 47023).

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P.B.B. served as a content developer and speaker for Rockpointe Corporation and FreeCe.com.

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