ORIGINAL ARTICLE

Clinical Risk Score for Prediction of Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* in Bloodstream Isolates

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OBJECTIVE. To develop a risk score to predict probability of bloodstream infections (BSIs) due to extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBLE).

DESIGN. Retrospective case-control study.

SETTING. Two large community hospitals.

PATIENTS. Hospitalized adults with *Enterobacteriaceae* BSI between January 1, 2010, and June 30, 2015.

METHODS. Multivariate logistic regression was used to identify independent risk factors for ESBLE BSI. Point allocation in extended-spectrum β-lactamase prediction score (ESBL-PS) was based on regression coefficients.

RESULTS. Among 910 patients with *Enterobacteriaceae* BSI, 42 (4.6%) had ESBLE bloodstream isolates. Most ESBLE BSIs were community onset (33 of 42; 79%), and 25 (60%) were due to *Escherichia coli*. Independent risk factors for ESBLE BSI and point allocation in ESBL-PS included outpatient procedures within 1 month (adjusted odds ratio [aOR], 8.7; 95% confidence interval [CI], 3.1–22.9; 1 point), prior infections or colonization with ESBLE within 12 months (aOR, 26.8; 95% CI, 7.0–108.2; 4 points), and number of prior courses of β-lactams and/or fluoroquinolones used within 3 months of BSI: 1 course (aOR, 6.3; 95% CI, 2.7–14.7; 1 point), ≥2 courses (aOR, 22.0; 95% CI, 8.6–57.1; 3 points). The area under the receiver operating characteristic curve for the ESBL-PS model was 0.86. Patients with ESBL-PSs of 0, 1, 3, and 4 had estimated probabilities of ESBLE BSI of 0.7%, 5%, 24%, and 44%, respectively. Using ESBL-PS ≥3 to indicate high risk provided a negative predictive value of 97%.

CONCLUSIONS. ESBL-PS estimated patient-specific risk of ESBLE BSI with high discrimination. Incorporation of ESBL-PS with acute severity of illness may improve adequacy of empirical antimicrobial therapy and reduce carbapenem utilization.

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Bloodstream infection (BSI) is the seventh leading cause of death in the United States, costing 75,000 lives annually; gram-negative bacilli account for ~50% of these cases.[1,2] Extended-spectrum β-lactamase (ESBL) production is among the most clinically concerning antimicrobial resistance mechanisms of gram-negative bacilli.[3,4]

The incidence of infections due to ESBL-producing *Enterobacteriaceae* (ESBLE) in the United States has increased recently in both community and tertiary-care hospitals.[5,6] More recently, the site of acquisition for most ESBLE infections has been community-onset rather than nosocomial, making these infections less predictable.[5]

Carbapenems are considered the treatment of choice for BSI due to ESBLE.[7] There is concern that the increase in incidence of ESBLE infections in the community may prompt an increase in carbapenem utilization, which may in turn contribute to further development of antimicrobial resistance and the spread of carbapenem-resistant *Enterobacteriaceae* (CRE).[8]

Stratification of patients based on predicted risk of ESBLE BSI provides a valuable tool for clinical providers to guide empirical antimicrobial therapy. Identification of patients at high risk of ESBLE BSI may improve adequacy of empirical antimicrobial therapy and, subsequently, patient outcomes.[9,10] In addition, such stratification may spare patients with low risk

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PREVIOUS PRESENTATION: The preliminary results of this study were presented in part at the American Society for Microbiology Microbe conference on June 20, 2016, in Boston, Massachusetts (Abstract no. MO-127).

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of ESBLE BSI from unnecessary carbapenems or other broad-spectrum agents.

In this case-control study, we aimed to develop a clinical score that predicts the risk of ESBLE BSI using prior antibiotic exposure and other clinical variables that are available at the time of initial presentation.

METHODS

Settings

The study was conducted at Palmetto Health Richland and Baptist Hospitals in Columbia, South Carolina. The 2 hospitals provide care to local residents of Richland County and receive referrals from nearby counties. The Institutional Review Board at Palmetto Health approved the study and waived informed consent.

Definitions

The site of infection acquisition was classified as community-acquired, healthcare-associated or hospital-acquired as previously defined.[11] Outpatient procedures included both invasive procedures (bladder, colon, and prostate biopsies, etc.) and noninvasive procedures (colonoscopy, cystoscopy, duodenoscopy, etc.) within 30 days of index BSI.[12] Prior infections or colonization with ESBLE was defined as documented growth of ESBLE in any clinical culture site in both inpatient and ambulatory settings within 12 months prior to index BSI. Prior β-lactam and fluoroquinolone exposure was defined as receiving >24 hours of the respective class of antimicrobial agents within 3–90 days prior to collection of index blood culture. Multiple courses of antibiotics had to be at least 72 hours apart. Concurrent therapy with a β-lactam and a fluoroquinolone or sequential therapy with these agents within 72 hours was considered 1 course of antibiotics. β-lactams included penicillins, cephalosporins, carbapenems, monobactam, and β-lactam/β-lactamase inhibitors. Receipt of prior antibiotics was ascertained from medication administration records from current and prior hospitalizations, clinical notes from current or prior visits (including emergency department, hospital admission, discharge summary, and consultation notes), and electronic prescriptions in medical records from prior visits to affiliated hospitals or ambulatory clinics.

Case Ascertainment

All adult patients with monomicrobial BSIs due to *Enterobacteriaceae* from January 1, 2010, to June 30, 2015, were identified through microbiology laboratory databases at Palmetto Health (n = 1,102). Recurrent episodes of BSI due to same or different *Enterobacteriaceae* during the study period were excluded (n = 38) to ensure that cases and controls were independent of each other, as assumed by the statistical hypothesis. Chromosomally mediated AmpC-producing *Enterobacteriaceae* (n = 153), including *Enterobacter*, *Citrobacter*, *Serratia*, *Providencia* and *Morganella* spp., and CRE (n = 1) were also excluded due to potential overlap between risk factors for BSI due to these pathogens and ESBLE.[13] The remaining 910 unique patients with first episodes of BSI due to *Escherichia coli, Klebsiella* spp., *Proteus mirabilis,* and *Salmonella* spp. were included in the study. Screening for ESBL production using the disk diffusion method with cefotaxime/clavulanate combination disks was performed in bloodstream isolates that were determined to be nonsusceptible *in vitro* to any tested third-generation cephalosporin according to Clinical and Laboratory Standards Institute criteria. Surveillance for CRE was available at both hospitals. *In vitro* antimicrobial susceptibility testing for carbapenems was routinely performed on all *Enterobacteriaceae* bloodstream isolates throughout the study period. In addition, PCR for KPC gene was performed on all bloodstream isolates from October 1, 2014, until the end of the study.

Statistical Analysis

Logistic regression was used to identify risk factors for ESBL production among *Enterobacteriaceae* bloodstream isolates in this case-control study. Demographics and clinical variables were collected for patients with BSI due to ESBLE (cases) and *Enterobacteriaceae* without ESBL production (controls). Prior antibiotic use was analyzed as a categorical variable: none, 1, or ≥2 courses of β-lactams and/or fluoroquinolones. Variables that were associated with ESBLE in the univariate analysis with $P < .10$ were included in multivariate logistic regression. Risk factors were retained in the final model if they were independently associated with ESBLE, with $P < .05$ in multivariate logistic regression using likelihood ratio test and individually if they were retained in ≥95% of 200 bootstrap samples. Each bootstrap sample was derived by applying the same model entry and retention criteria.

The ESBL prediction score (ESBL-PS) was derived from the final model. Points were assigned for each independent risk factor and weighted approximately by the corresponding regression coefficients. Area under receiver operating characteristic curve (AUC) was used to quantify the discriminative ability of ESBL-PS; a value of 0.5 denoted random predictions and a value of 1.0 denoted perfect predictions.

In addition to bootstrap resampling, model calibration was examined to internally validate the model. Deciles of predicted risk of ESBLE BSI were plotted from the ESBL-PS model by the actual fraction of patients who had BSI due to ESBLE to visually access calibration. The performance characteristics of the ESBL-PS as a binary classification test were examined. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated from the receiver operating characteristic curve for the best cutoff points.

JMP Pro version 12.0 (SAS Institute, Cary, NC) was used for statistical analyses. The level of significance for statistical testing was $P < .05$ (2-sided) unless otherwise specified.

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RESULTS

Demographics, Clinical Characteristics, and Microbiology

During the study period, 910 patients with *Enterobacteriaceae* BSI were included in the study. Overall, their median age was 66 years, and 401 patients (44%) were men. *Escherichia coli* (n = 597; 66%) was the most common bloodstream isolate overall, followed by *K. pneumoniae* (n = 211; 23%), *P. mirabilis* (n = 78; 9%), *K. oxytoca* (n = 14; 2%), and *Salmonella* species (n = 10; 1%).

Among *Enterobacteriaceae* bloodstream isolates, 42 (4.6%) demonstrated ESBL production. *Escherichia coli* was also the most common ESBLE (n = 25; 60%), followed by *K. pneumoniae* (n = 15; 36%) and *K. oxytoca* (2; 5%). Most ESBLE BSIs were acquired outside the hospital (n = 33; 79%), including 12 community-acquired BSIs (29%) and 21 healthcare-associated BSIs (50%). The baseline demographics and clinical characteristics of patients in the ESBLE and control groups are shown in Table 1.

TABLE 1. Demographics and Clinical Characteristics of patients With Bloodstream Infections Due to *Enterobacteriaceae*

Variable	ESBLE, No. (%) (n = 42)	Non-ESBLE, No. (%) (n = 868)
Age, y, median (IQR)	65 (49–71)	66 (55–78)
Male sex	24 (57)	377 (43)
Ethnicity		
White	20 (48)	408 (47)
African American	18 (43)	434 (50)
Other	4 (10)	26 (3)
Diabetes mellitus	15 (36)	322 (37)
End-stage renal disease	4 (10)	72 (8)
Liver cirrhosis	2 (5)	42 (5)
Cancer	10 (24)	141 (16)
Immune compromised host	4 (10)	99 (11)
Hospital-acquired infection	9 (21)	160 (18)
Recent hospitalization[a]	23 (55)	248 (29)
Residence at skilled nursing facility	10 (24)	139 (16)
Indwelling urinary catheterization	9 (21)	87 (10)
Indwelling central venous catheter	11 (26)	142 (16)
Recent chemotherapy[b]	3 (7)	65 (7)
Recent outpatient procedure[b]	7 (17)	43 (5)
Prior infections/colonization with ESBLE[c]	9 (21)	6 (1)
No. of prior courses of BL/FQ[a]		
0	14 (33)	709 (82)
1	13 (31)	128 (15)
≥2	15 (36)	31 (4)

NOTE. ESBLE, extended-spectrum β-lactamase–producing *Enterobacteriaceae*; IQR, interquartile range; BL, β-lactams; FQ, fluoroquinolones.
Data shown as number (%) unless otherwise specified.
[a]Within 90 days of bloodstream infection.
[b]Within 30 days of bloodstream infection.
[c]Within 365 days of bloodstream infection.

Risk Factors for BSI Due to ESBLE

In univariate logistic regression, male sex, recent hospitalization, indwelling urinary catheters, recent outpatient procedures, prior infections or colonization with ESBLE, and prior antibiotics were associated with ESBLE. Notably, nosocomial acquisition was not associated with ESBLE (Table 2).

After adjustments in the multivariate model, male sex (adjusted odds ratio [aOR], 1.6; 95% confidence intervals [CI], 0.8–3.4; $P = .18$), recent hospitalization (aOR, 1.0; 95% CI, 0.4–2.3; $P = .98$), and indwelling urinary catheters (aOR, 1.5; 95% CI, 0.6–3.5; $P = .40$) were not independently associated with ESBLE BSI. Recent outpatient procedures, prior infections or colonization with ESBLE, and prior exposure to antibiotics were independently associated with ESBLE BSI (Table 3).

Development and Internal Validation of ESBL Prediction Score

All 3 variables that were independently associated with ESBLE BSI were retained in ≥95% of bootstrap samples and were

TABLE 2. Univariate Logistic Regression Results for Risk Factors of Bloodstream Infection Due to Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* (ESBLE)

Variable	OR	(95% CI)	*P* Value
Age (per decade)	0.9	(0.8–1.1)	.19
Male sex	1.7	(0.9–3.3)	.08
White ethnicity	1.0	(0.6–1.9)	.94
Diabetes mellitus	0.9	(0.5–1.8)	.86
End-stage renal disease	1.2	(0.3–3.0)	.78
Liver cirrhosis	1.0	(0.2–3.4)	.98
Cancer	1.6	(0.7–3.2)	.22
Immune compromised host	0.8	(0.2–2.1)	.70
Hospital-acquired infection	1.2	(0.5–2.5)	.63
Recent hospitalization[a]	3.0	(1.6–5.7)	<.001
Residence at skilled nursing facility	1.6	(0.8–3.3)	.20
Indwelling urinary catheterization	2.5	(1.1–5.1)	.03
Indwelling central venous catheter	1.8	(0.9–4.0)	.12
Recent chemotherapy[b]	1.0	(0.2–2.7)	.95
Recent outpatient procedure[b]	3.7	(1.5–8.5)	.008
Prior infections/colonization with ESBLE[c]	39.2	(13.4–123.1)	<.001
No. of prior courses of BL/FQ[a]			
0	1.0	(Reference)	
1	5.1	(2.3–11.3)	<.001
≥2	24.5	(10.9–55.9)	<.001

NOTE. OR, odds ratio; CI, confidence interval; BL, β-lactams; FQ, fluoroquinolones.
[a]Within 90 days of bloodstream infection.
[b]Within 30 days of bloodstream infection.
[c]Within 365 days of bloodstream infection.

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TABLE 3. Independent Risk Factors of Bloodstream Infection Due to Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae (ESBLE) and Point Allocation in ESBL Prediction Score

Variable	aOR	(95% CI)	*P* Value	Point Allocation
Recent outpatient GI/GU procedure[a]	8.6	(3.0–22.5)	<.001	1
No. of prior BL/FQ courses[b]				
0	1	Reference		0
1	6.3	(2.7–14.7)	<.001	1
≥2[c]	22.1	(8.6–57.2)	<.001	3
Prior infections/colonization with ESBLE[d]	26.8	(7.0–108.2)	<.001	4

NOTE. aOR: adjusted odds ratio; CI: confidence interval; GI: gastrointestinal; GU: genitourinary; BL: β-lactams; FQ: fluoroquinolones.
[a]Within 30 days of bloodstream infection.
[b]Within 3 to 90 days of bloodstream infection.
[c]Multiple courses of antibiotics are given at least 3 days apart.
[d]Within 365 days of bloodstream infection.

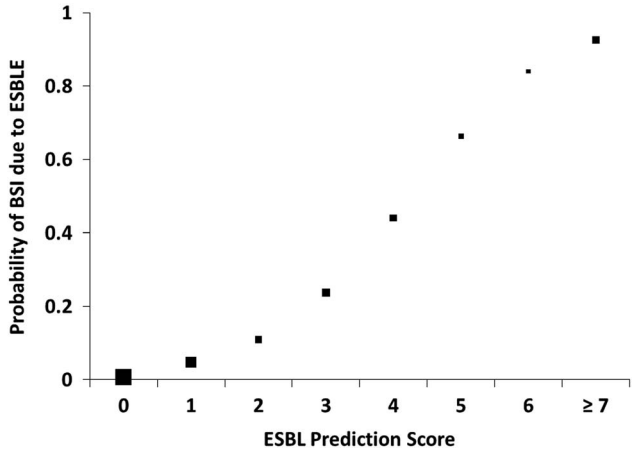

FIGURE 1. Estimated probability of bloodstream infection due to extended-spectrum β-lactamase *Enterobacteriaceae* (ESBLE) based on ESBL prediction score. Size of marker is approximately proportional to number of subjects with that particular score. BSI, bloodstream infection.

included in the final model. The AUC for the final logistic regression model was 0.86. The ESBL prediction score (ESBL-PS) was developed by assigning points for each risk factor in the final model, weighted approximately by the corresponding regression coefficients (Table 3). The ESBL-PS is the cumulative number of points for each individual from their risk factors, and ranges from 0 to 8. The AUC for the ESBL-PS was 0.86 (Supplementary Figure 1). Model calibration was satisfactory; the observed outcomes were fairly close to the predictions (Supplementary Figure 2).

The ESBL-PS equips clinicians with a tool with which to predict the risk of ESBLE BSI (Figure 1). A higher score corresponds to an increased risk of ESBLE BSI. For example, patients with an ESBL-PS of 0 have <1% predicted probability of ESBLE BSI. The estimated risk increases to >20% and >50% in patients with ESBL-PSs of 3 and 5, respectively.

The performance characteristics of the ESBL-PS as a binary classification test for selected cutoff points are shown in Table 4. Using a cutoff score ≥3 to indicate high risk of ESBLE BSI provided the best performance in the statistical model with a NPV of 97%. A more conservative approach using a cutoff score ≥1 improved sensitivity and NPV to 88% and 99%, respectively, at the expense of specificity and PPV.

TABLE 4. Performance of Extended-Spectrum β-Lactamase (ESBL) Prediction Score as a Binary Classification Test

ESBL-PS	Sensitivity, %	Specificity, %	PPV, %	NPV, %
≥1	88	77	16	99
≥3[a]	43	96	33	97

NOTE: ESBL-PS, ESBL prediction score; PPV, positive predictive value; NPV, negative predictive value.
[a]Using an ESBL-PS ≥3 to indicate high predicted risk of bloodstream infection due to ESBL-producing *Enterobacteriaceae* provides the best performance in statistical model.

DISCUSSION

Independent Risk Factors for ESBLE BSI

The results of this study demonstrate that the risk of BSI due to ESBLE can be estimated with high discrimination based on prior antibiotic exposure, prior infections or colonization with ESBLE, and recent outpatient procedures.

The association between recent antibiotic use and ESBLE infections has been well established in previous studies.[3,4,14–16] In the current study, we used a novel approach of categorizing this variable by the number of antibiotic courses received within the prior 90 days. This method improved model discrimination due to considerably higher risk of ESBLE BSI within a smaller proportion of patients who received multiple courses of antibiotics compared to those who received only 1 prior course. Identification of prior infections or colonization with ESBLE within the prior 12 months as the strongest risk factor for ESBLE BSI was consistent with the results of a large investigation in Netherlands.[15] Recent outpatient genitourinary and gastrointestinal procedures have been associated with increased risk of acquisition of bacteria that harbor antimicrobial resistance.[12,17,18] The increased risk of ESBLE BSI following these procedures calls for improvements in infection control practices in these settings.

Clinical Applications of ESBL-PS

The implementation of the ESBL-PS into workflow practices of healthcare providers is feasible due to the small number and accessibility of these variables. Some risk factors may be

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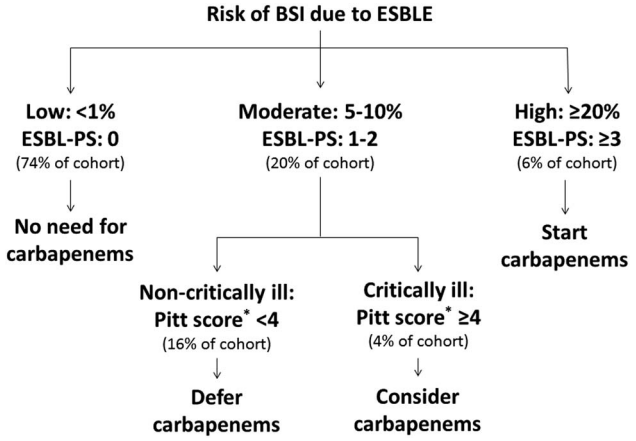

FIGURE 2. Proposed algorithm for application of extended-spectrum β-lactamase (ESBL) prediction score in management of bloodstream infections. BSI, bloodstream infection; ESBL-PS, extended-spectrum β-lactamase prediction score.* Patterson DL, et al. *Ann Intern Med* 2004;140:26–32.

displayed in real time in electronic medical records (ie, prior infections or colonization with ESBLE); other data (ie, prior antibiotics or outpatient procedures) may be collected in a patient interview or quickly obtained from the electronic medical record if the patient is unable to communicate.

Application of the ESBL-PS provides clinicians with opportunities to improve both empirical antimicrobial therapy and carbapenem utilization. The ESBL-PS categorizes patients based on predicted risk of ESBLE BSI into 3 risk groups: low, moderate, and high (Figure 2). Low-risk patients have no risk factors; moderate-risk patients are those with minor risk factors such as an outpatient procedure or 1 prior course of antibiotics; and high-risk patients are those with major risk factors such as prior infections or colonization with ESBLE or multiple courses of antibiotics. The decision to withhold carbapenem therapy was straightforward in nearly 75% of patients in the cohort who had low predicted probability of ESBLE BSI. Similarly, empirical carbapenem therapy appears to have been appropriate in the high-risk group, which represented 6% of the study cohort; however, prescription of carbapenems to the remaining 20% of patients in the moderate-risk group does not appear to have been a high-yield intervention. To improve the benefit-to-risk ratio of antimicrobial therapy, the stratification of the moderate-risk group further is suggested, according to the acute severity of illness using the Pitt bacteremia score[19] or the predicted prognosis using the BSI mortality risk score (BSIMRS).[20,21] Because survival benefit from adequate empirical antimicrobial therapy has been clearly demonstrated in critically ill patients (Pitt bacteremia score ≥4) and those with guarded prognosis at initial presentation (ie, BSIMRS ≥5),[10] carbapenem therapy may be justified in those patients in the moderate-risk group. Application of the proposed algorithm results in the exposure of only 10% of patients to carbapenems (which is nearly twice the overall incidence of ESBLE among bloodstream isolates in the current study) while providing adequate empirical therapy to ~98% of overall cohort and >99% of critically ill patients. It is reassuring that this improvement in the adequacy of empirical therapy will not result in an increase in overall carbapenem utilization, even in institutions with existing carbapenem restrictions (like the 2 hospitals included in this study). In the current cohort of 910 patients, 92 (10.1%) received empirical carbapenem therapy, including 9 of 42 (21.4%) in the ESBLE and 83 of 868 (9.6%) in the control group. Modification of institutional criteria for empirical carbapenem use according to the proposed algorithm is justified because it allows for earlier appropriate therapy in high-risk patients without an increase in overall carbapenem use.

Changing Epidemiology of ESBLE BSI

Since ESBLEs were first reported in 1983,[22] prolonged hospitalization has been considered among the most important risk factors for harboring these organisms.[3,4] However, ESBLEs have emerged as community-onset pathogens since the beginning of this century,[23,24] and they have recently been reported with increasing frequency in community-onset infections in North America and Europe.[5,6,25] The current study confirms that most ESBLE BSIs are acquired outside the hospital and that nosocomial acquisition is not a risk factor for ESBLE in this setting. We suspect that the widespread use of broad-spectrum antibiotics in the community (both orally and intravenously) and improvements in infection control practices in hospitals have shifted most ESBLE infections to the community-onset setting. In addition, *E. coli* has surpassed *Klebsiella* spp. to become the most common ESBLE.[5,6] The ability of *E. coli*, particularly sequence type 131, to adapt to local environments and spread in the community poses serious challenges to the healthcare system.[26,27] Moreover, the widespread dissemination of the CTX-M-15 genotype among *E. coli* sequence type 131 in the southeastern United States requires an urgent call to change antibiotic prescription practices in the community.[28,29] Efforts to minimize unnecessary prescription of antibiotics, particularly β-lactams and fluoroquinolones, in outpatient settings should be emphasized.[30]

The main strength of this study is the inclusion of patients from 2 community hospitals in addition to data from inpatient and outpatient procedure records, prior culture results, and antibiotic prescriptions from several affiliated hospitals, emergency rooms, urgent treatment centers, and outpatient clinics in the area.[31] Despite the limitations of retrospective design, only 5 of 42 patients with ESBLE BSIs did not have identifiable risk factors. Of these 5 patients, 2 were temporary visitors with recent international travel and no documentation of prior culture results, antibiotic exposures, or procedures in medical records. Another 2 were transferred from nearby medical facilities with incomplete transfer records of

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administered medications. Transfers from other healthcare facilities within the same country and receiving healthcare internationally have been associated with increased risk of harboring ESBLE in prior studies,[14,32] likely due to uncaptured prior antibiotic exposure, procedures, and culture results. Antimicrobial stewardship programs should explore educating healthcare providers regarding the value of inquiring about prior antibiotic use upon selection of empirical therapy for potentially life-threatening infections. Requesting records of medications, procedures, and prior culture results of patients transferred to tertiary care hospitals is equally important. Second, due to the relatively small number of ESBLE BSI, the study may have lacked power to identify other minor risk factors with equal or less weight to outpatient procedures or 1 course of antibiotics. Third, the model was derived from 2 hospitals within the same healthcare system and geographical location. Data from multiple settings may provide external validity and generalizability. Finally, molecular testing was not performed on bloodstream isolates to identify CTX-M or other ESBL genotypes.

In the era of increasing antimicrobial resistance among community-onset bacterial isolates, efforts to improve utilization of currently available antibiotics and to prevent further induction of antimicrobial resistance are of vital importance. Prediction of ESBLE based on patient-specific risk factors provides an alternative solution to the nonstratified use of carbapenems for the general fear of ESBLE infections. The ESBL-PS allows healthcare providers to stratify patients based on estimated risk of BSI due to ESBLE with high discrimination. Application of the ESBLE-PS based on acute severity of illness may improve the adequacy of empirical antimicrobial therapy without increasing carbapenem utilization.

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M.N.A. is on the continuous medical education steering committee for Rockpointe Corporation, Columbia, Maryland. All other authors report no conflicts of interest.

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2016.292

REFERENCES

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect* 2013;19:501–509.
2. Uslan DZ, Crane SJ, Steckelberg JM, et al. Age-and sex-associated trends in bloodstream infection. *Arch Intern Med* 2007;167: 834–839.
3. Jacoby GA. Extended-spectrum beta-lactamases and other enzymes providing resistance to oxyimino-beta-lactams. *Infect Dis Clin North Am* 1997;11:875–887.
4. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev* 2005;18:657–686.
5. Thaden JT, Fowler VG, Sexton DJ, Anderson DJ. Increasing incidence of extended-spectrum β-lactamase-producing *Escherichia coli* in community hospitals throughout the southeastern United States. *Infect Control Hosp Epidemiol* 2016;37:49–54.
6. Kassakian SZ, Mermel LA. Changing epidemiology of infections due to extended spectrum beta-lactamase producing bacteria. *Antimicrob Resist Infect Control* 2014;3:9.
7. Tamma PD, Han JH, Rock C, et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. *Clin Infect Dis* 2015;60:1319–1325.
8. Orsi GB, Bencardino A, Vena A, et al. Patient risk factors for outer membrane permeability and KPC-producing carbapenem-resistant *Klebsiella pneumoniae* isolation: results of a double case-control study. *Infection* 2013;41:61–67.
9. Retamar P, Portillo MM, López-Prieto MD, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. *Antimicrob Agents Chemother* 2012;56:472–478.
10. Cain SE, Kohn J, Bookstaver PB, Albrecht H, Al-Hasan MN. Stratification of the impact of inappropriate empirical antimicrobial therapy for gram-negative bloodstream infections by predicted prognosis. *Antimicrob Agents Chemother* 2015;59:245–250.
11. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;137:791–797.
12. Dan S, Shah A, Justo JA, et al. Prediction of fluoroquinolone resistance in Gram-negative bacteria causing bloodstream infections. *Antimicrob Agents Chemother* 2016;60:2265–2272.
13. Hammer KL, Stoessel A, Justo JA, et al. Association between chronic hemodialysis and bloodstream infections due to chromosomally-mediated AmpC-producing Enterobacteriaceae. *Am J Infect Control* 2016. doi: 10.1016/j.ajic.2016.05.017 [Epub ahead of print].
14. Tumbarello M, Trecarichi EM, Bassetti M, et al. Identifying patients harboring extended-spectrum-β-lactamase-producing Enterobacteriaceae on hospital admission: derivation and validation of a scoring system. *Antimicrob Aagents Chemother* 2011;55:3485–3490.
15. Rottier WC, Bamberg YR, Dorigo-Zetsma JW, van der Linden PD, Ammerlaan HS, Bonten MJ. The predictive value of prior colonization and antibiotic use for 3rd generation cephalosporin resistant Enterobacteriaceae bacteremia in patients with sepsis. *Clin Infect Dis* 2015;60:1622–1630.
16. Ben-Ami R, Rodríguez-Baño J, Arslan H, et al. A multinational survey of risk factors for infection with extended-spectrum

beta-lactamase-producing Enterobacteriaceae in nonhospitalized patients. *Clin Infect Dis* 2009;49:682–690.
17. Williamson DA, Roberts SA, Paterson DL, et al. *Escherichia coli* bloodstream infection after transrectal ultrasound-guided prostate biopsy: implications of fluoroquinolone-resistant sequence type 131 as a major causative pathogen. *Clin Infect Dis* 2012;54:1406–1412.
18. Epstein L, Hunter JC, Arwady MA, et al. New Delhi metallo-β-lactamase-producing carbapenem-resistant *Escherichia coli* associated with exposure to duodenoscopes. *JAMA* 2014;312:1447–1455.
19. Patterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM. International prospective study of *Klebsiella pneumoniae* bacteraemia: implications of extended-spectrum β-lactamase production in nosocomial infections. *Ann Intern Med* 2004;140:26–32.
20. Al-Hasan MN, Lahr BD, Eckel-Passow JE, Baddour LM. Predictive scoring model of mortality in gram-negative bloodstream infection. *Clin Microbiol Infect* 2013;19:948–954.
21. Al-Hasan MN, Juhn YJ, Bang DW, Yang HJ, Baddour LM. External validation of gram-negative bloodstream infection mortality risk score in a population-based cohort. *Clin Microbiol Infect* 2014;20:886–891.
22. Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of Klebsiella pneumoniae and Serratia marcescens. *Infection* 1983;11:315–317.
23. Rodríguez-Baño J, Navarro MD, Romero L, et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in nonhospitalized patients. *J Clin Microbiol* 2004;42:1089–1094.
24. Pitout JD, Hanson ND, Church DL, Laupland KB. Population-based laboratory surveillance for *Escherichia coli*–producing extended-spectrum beta-lactamases: importance of community isolates with blaCTX-M genes. *Clin Infect Dis* 2004;38:1736–1741.
25. Courpon-Claudinon A, Lefort A, Panhard X, Clermont O, Dornic Q, Fantin B, et al. Bacteraemia caused by third-generation cephalosporin-resistant Escherichia coli in France: prevalence, molecular epidemiology and clinical features. *Clin Microbiol Infect* 2011;17:557–565.
26. Nicolas-Chanoine MH, Bertrand X, Madec JY. *Escherichia coli* ST131, an intriguing clonal group. *Clin Microbiol Rev* 2014;27:543–574.
27. Banerjee R, Johnston B, Lohse C, et al. The clonal distribution and diversity of extraintestinal *Escherichia coli* isolates vary according to patient characteristics. *Antimicrob Agents Chemother* 2013;57:5912–5917.
28. Hayakawa K, Gattu S, Marchaim D, et al. Epidemiology and risk factors for isolation of *Escherichia coli*–producing CTX-M-type extended-spectrum β-lactamase in a large US Medical Center. *Antimicrob Agents Chemother* 2013;57:4010–4018.
29. Chen LF, Freeman JT, Nicholson B, et al. Widespread dissemination of CTX-M-15 genotype extended-spectrum-β-lactamase-producing Enterobacteriaceae among patients presenting to community hospitals in the southeastern United States. *Antimicrob Agents Chemother* 2014;58:1200–1202.
30. Meeker D, Linder JA, Fox CR, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: a randomized clinical trial. *JAMA* 2016;315:562–570.
31. Kutob LF, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Effectiveness of oral antibiotics for definitive therapy of gram-negative bloodstream infections. *Int J Antimicrob Agents* 2016;48:498–503.
32. Goodman KE, Lessler J, Cosgrove SE, et al. A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamase-producing organism. *Clin Infect Dis* 2016;63:896–903.

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