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ORIGINAL RESEARCH

Infectious Disease

Characterization of predictors of ESBL-producing enterobacteriaceae in urine cultures of emergency department patients

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Abstract

Study objective: With increasing prevalence of extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBLE), more reliable identification of predictors for ESBLE urinary tract infection (UTI) in the emergency department (ED) is needed. Our objective was to evaluate risk factors and their predictive ability for ED patients with ESBLE UTI.

Methods: This was a retrospective case-control study at an urban academic medical center. Microbiology reports identified adult ED patients with positive urine cultures from 2015–2018. Inclusion criteria were diagnosis of UTI with monomicrobial enterobacteriaceae culture growth. Exclusions were cultures with carbapenemase-resistant enterobacteriaceae or urinary colonization. Collected variables included demographics, comorbidities, and recent medical history. Patient disposition, urine culture susceptibilities, presence of ESBLE, empiric antibiotics, and therapy modifications were collected. Patients were stratified based on ESBLE status and analyzed via descriptive statistics. The data were divided into 2 parts: the first used to identify possible predictors of ESBLE UTI and the second used to validate an additive scoring system.

Results: Of 466 patients, 16.3% had ESBLE urine culture growth and 83.7% did not; 39.5% of ESBLE patients required antibiotic therapy modification, as compared to 6.4% of ESBLE negative patients (odds ratio [OR] 9.5; confidence interval [CI] 8.9–10.1). Independent predictors of ESBLE UTI were IV antibiotics within 1 year (OR 5.4; CI 2.1–12.8), surgery within 90 days (OR 6.4; CI 1.5–27.8), and current refractory UTI (OR 8.5; CI 2.0–36.6).

Conclusion: Independent predictors of ESBLE UTI in emergency department patients included IV antibiotics within 1 year, surgery within 90 days, and current refractory UTI.

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1 | INTRODUCTION

1.1 | Background

Urinary tract infections (UTIs) were the primary diagnosis for over 2 million emergency department visits in 2015.[1] Prevalence of extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBLE) in UTIs are increasing.[2–4] As a result, more patients are at risk for inadequate empiric therapy, leading to potential treatment failure, prolonged hospital stays, and greater costs of care.[5–8] ESBLE can express resistance to all beta-lactam antibiotics except certain beta-lactam/beta-lactamase inhibitor combinations or carbapenems. Additionally, ESBLE may possess additional mechanisms of resistance against antibiotics frequently prescribed for UTIs including fluoroquinolones and trimethoprim-sulfamethoxazole.[9,10] In these instances, carbapenems may become a necessary drug of choice.[11]

1.2 | Importance

Although local antibiograms offer valuable insight in the selection of empiric antimicrobial therapy, wide variability in acuity and risk factors in patients presenting to the ED can lead to variable concordance with antimicrobial susceptibilities in patient subgroups.[7,8] This makes it important for the clinician to assess risk for ESBLE based on patient-specific factors in order to determine the most appropriate empiric antimicrobial therapy. In bloodstream infections, several tools have been developed for this purpose, including a clinical decision tree and risk scoring system based on risk factors for ESBLE. These studies specifically identify a history of ESBLE, chronic indwelling catheter use, recent gastrointestinal or genitourinary procedure, prior beta-lactam or fluoroquinolone use, and age as critical risk factors for ESBLE bloodstream infections.[12,13]

1.3 | Goals of this investigation

In a recent study, nearly half of patients with ESBLE UTI presenting in the ED had no identifiable risk factors and nearly 80% received discordant empiric antimicrobial therapy.[14] More reliable identification of risk factors for ESBLE UTI in the ED is needed to better direct empiric antibiotic therapy. The objective of our study was to evaluate risk factors and their predictive ability for patients with ESBLE UTI presenting to the ED.

2 | METHODS

2.1 | Study design and population

We conducted a single-center retrospective case-control study at an urban academic medical center in New Jersey. This study was approved by the institutional review board. Patients with positive urine

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> **The Bottom Line**
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> Patients frequently present to the ED to be evaluated and empirically treated for urinary tract infections (UTIs); however, extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBLE) have become more common. In this study, IV antibiotics in the prior year, surgery within 90 days, or persistent urinary symptoms despite active with treatment with antibiotics were independent predictors of ESBLE UTI.

cultures collected between 2015 and 2018 in the ED were identified through a microbiology report. Patients were included if they were ages 18 years or older, diagnosed with a UTI in the ED, and had a urine culture drawn in the ED growing enterobacticeae with antimicrobial susceptibilities reported. Enterobactericeae included were *Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*, *Serratia spp.*, *Proteus spp.*, *Providencia spp.*, and *Citrobacter spp.* ESBLE cultures were identified by Phoenix testing. The Phoenix instrument uses antimicrobial susceptibility testing results for ceftazidime, ceftriaxone/clavulanate, cefotaxime/clavulanate, ceftazidime/clavulanate, cefpodoxime, and cefepime along with an expert system to detect and confirm presence of ESBL. Patients were excluded if the culture resulted in polymicrobial growth, carbapenem-resistant enterobacteriaceae, or enterobacteriaceae urinary colonization. Urinary colonization was determined based on physician's or physician assistant's clinical judgement, that is, urinary culture growth without documented diagnosis of an active UTI. Duplicate records were also excluded, that is, only the first recorded UTI per patient was included.

At our institution, emergency medicine pharmacy residents manage a culture follow-up program. The pharmacist runs a report to identify patients discharged with positive culture data. For patients receiving discordant therapy based on susceptibility results, the pharmacist and an attending emergency physician create a plan that may include a follow-up phone call to the patient, alternative antibiotic therapy, or recommendation of reevaluation. If the pharmacist is unable to reach the patient via phone, certified letters are sent to the patient's listed address.

2.2 | Data collection

Previous studies were reviewed to identify possible predictor variables for data collection.[3,5,12,14–18] Variables collected included patient demographics, comorbidities, and recent medical history including recent hospitalizations, surgeries, antibiotic use, and immunosuppressant use. History of recurrent UTI was defined as 2 or more UTIs within 6 months, 3 or more within 12 months, or documentation of recurrent UTI diagnosis in patients' past medical history[19]. Current refractory UTI was defined as patients presenting to the ED with unresolved symptoms despite reported outpatient antimicrobial use. Patient

disposition, urine culture susceptibilities, presence of ESBL resistance in urine culture growth, empiric antibiotic treatment, and modifications to empiric antibiotic therapy were also collected.

Data abstraction was completed by clinically trained abstractors (E.Z. and R.S.), and a sample of charts were reviewed independently by 2 additional clinically trained abstractors (P.B. and N.N.) to ensure accuracy. Data points were precisely defined to minimize subjectivity, and any missing or ambiguous points were discussed by the team of abstractors until a consensus decision was made.

2.3 | Statistics

Initial descriptive statistics on patients with ESBLE positive and ESBLE negative cultures were calculated on the entire data set. ESBLE positive patients were designated as cases, and ESBLE negative patients were designated as controls. A 2-sided t test or chi square test was used to calculate the P value.

We then randomly divided the data set into 2 equal parts: the training set to build a model and the test set to confirm validity of the identified model. To build the model using the training set, we identified critical predictors for ESBLE using 5-fold external cross-validations, with a least absolute shrinkage and selection operator (LASSO) selection of predictors in a general linear model (GLMSELECT in SAS/STAT Enterprise Guide for Windows, Version 7.15, Copyright 2017, SAS Institute Inc., Cary, NC, USA).[20,21] The method of cross-validation was used to avoid the problem of overfitting in the context of creating a model for prediction. Overfitting is less likely to occur with cross-validation as a model is fit on a portion of the data and then validated on another in an iterative way. This reduces the potential effect of a small number of observations leading to selection of one of the variables, because in various "folds" those observations will not be present.[17] The final model was validated using the test set of data.

The model building procedure used the LASSO for selection of predictors because of the large number of highly correlated predictors. Selection occurred stepwise by increasing the LASSO parameter to include larger numbers of covariates. We stopped increasing the number of predictors in the model when the cross-validated predicted residual error sum of squares (PRESS) statistic reached its minimum. The model building approach was based on a multiple regression model in which the mean response (ie, a probability of having ESBLE infection) is modeled as a linear function of the predictors. Because all but one of the predictors (age) are binary predictors, the predictors selected would be similar if we used model building with logistic regression.

For the testing of the model, we calculated the r^2 values for the final model as applied to the test data. We ran logistic regression with the identified predictors, using the test data, in order to estimate odds ratios describing the effects of the predictors. With the difference in modeling technique, we also rechecked whether age, our only continuous variable, contributed to predicting ESBL infection. A scoring system was developed based on the identified predictors. Using the entire data set, sensitivity and specificity for ESBLE UTI were calculated based on the developed scoring system.

All analyses were conducted with the SAS software.

3 | RESULTS

A total of 466 were included in the study. Seventy-six (16.3%) of patients had ESBLE urine culture growth (ESBL+ group), and 390 (83.7%) did not (ESBL- group). Table 1 describes the patient characteristics and clinical features of both groups. Based on descriptive statistics, there were statistically significant differences between the 2 groups with regard to past medical history of chronic kidney disease, renal transplant, history of any ESBLE infection within 1 year, any surgery within up to 90 days, genitourinary surgery within 30 days, hospital admission within 1 year, oral or IV antibiotic use within 1 year, current refractory UTI, and immunosuppressant use within 30 days. Ninety-two percent of patients included were discharged, and the most frequent antibiotics prescribed were cephalosporins, fluoroquinolones, and nitrofurantoin (Table 2). Patients were significantly more likely to require modification of antibiotic therapy at follow-up phone call in the ESBL+ group ($P < 0.001$).

A 5-fold external cross-validation was developed, as described in the methods section. The r^2 values for the training and test data sets were 0.16 and 0.14, respectively, indicating avoidance of overfitting and internal generalizability of the model beyond the training data. Based on this model, 3 variables were identified as independent predictors of ESBLE UTI: IV antibiotic administration within the last year, any surgery within the last 90 days, and current refractory UTI (Table 3).

Using the 3 identified predictors of ESBLE UTI, an additive scoring system was developed with a score of 1 assigned to each risk factor. The sensitivity and specificity of this scoring system were tested on the entire study population. Of note, no patients in our study had a score of 3. Sensitivity and specificity of the ESBLE UTI predictor scoring system were calculated with score cutoffs of 1 or 2 (Table 4). Eleven percent of patients with a score of 1 had an ESBLE UTI, and 85.1% with a score of 2 had an ESBLE UTI. In a population with 5% prevalence of ESBLE, a score cutoff of 2 points would have a 96.2% negative predictive value and a 5.3% positive predictive value. In a population with 10% prevalence of ESBLE, a score cutoff of 2 points would have a 92.4% negative predictive value and a 10.6% positive predictive value.

4 | LIMITATIONS

Our study had a few noteworthy limitations. Because of its retrospective nature, risk factor identification was limited to review of documentation and previous medical history at our hospital system (eg, previous culture history and patient reporting of previous resistant infections). Given the low incidence of several possible risk factors in our study thereby necessitating their exclusion from the predictor model, a larger study is recommended to further develop our ESBLE predictor score for UTIs in the ED. Additionally, over 80% of our patients were discharged, thereby limiting the applicability of this scoring system to patients admitted to the hospital.

TABLE 1 Demographic and clinical characteristics stratified by ESBLE infection status

Variable	ESBL+ (n = 76)	ESBL- (n = 390)	P value
Age (median)	47.6	40.4	
Male	16 (21.1)	62 (15.9)	NS
Comorbidities			
Cardiovascular disease	31 (40.8)	109 (27.9)	0.03
Cerebrovascular disease	6 (7.9)	16 (4.1)	NS
Chronic kidney disease	5 (6.6)	6 (1.5)	0.04
Cirrhosis[c]	1 (1.3)	2 (0.5)	NS
Diabetes mellitus	17 (22.4)	56 (14.4)	NS
Dialysis[c]	1 (1.3)	1 (0.3)	NS
Dementia	3 (3.9)	10 (2.6)	NS
Hematologic malignancy[c]	1 (1.3)	0 (0)	NS
Metastatic malignancy[c]	1 (1.3)	0 (0)	NS
Neutropenia[c]	0 (0)	1 (0.3)	NS
Pulmonary	8 (10.5)	35 (8.9)	NS
Renal colic	3 (3.95)	13 (3.3)	NS
Renal transplant	5 (6.6)	3 (0.8)	0.01
Recurrent UTI	8 (10.5)	32 (8.2)	NS
Solid organ malignancy	7 (9.2)	20 (5.1)	NS
Bedridden[c]	1 (1.3)	1 (0.3)	NS
History of ESBLE infection within 1 y	5 (6.6)	0 (0)	<0.001
Surgery within 1 y	14 (18.4)	20 (5.1)	<0.001
Surgery within 90 d	11 (14.5)	8 (2.1)	<0.001
Surgery within 30 d	8 (10.5)	8 (2.1)	0.003
GU surgery within 1 y	8 (10.5)	11 (2.8)	0.01
GU surgery within 90 d	6 (7.9)	4 (1.0)	0.003
GU surgery within 30 d	5 (6.6)	4 (1.0)	0.02
Nephrostomy tubes	5 (6.6)	6 (1.5)	0.04
GU catheter	4 (5.2)	18 (4.6)	NS
Venous catheter (eg, PICC, midline)	0 (0)	1 (0.3)	NS
Residence in nursing home	3 (3.9)	4 (1.0)	NS
Residence in long-term-care facility	0 (0)	4 (1.0)	NS
Hospital admission within 1 y	26 (34.2)	43 (11.0)	<0.001
Hospital admission within 90 d	10 (13.2)	18 (4.6)	0.02
Hospital admission within 30 d	7 (9.2)	9 (2.3)	0.02
ICU admission within 1 y[c]	1 (1.3)	1 (0.3)	NS
ICU admission within 90 d[c]	0 (0)	1 (0.3)	N/A
ICU admission within 30 d[c]	0 (0)	0 (0)	N/A
Oral antibiotics within 1 y	24 (31.6)	40 (10.3)	<0.01
Oral antibiotics within 90 d	12 (14.8)	20 (5.1)	<0.001
Oral antibiotics within 30 d	7 (9.2)	15 (3.8)	NS
IV antibiotics within 1 y	20 (26.3)	26 (6.7)	<0.001
IV antibiotics within 90 d	7 (9.2)	13 (3.3)	NS
IV antibiotics within 30 d	6 (7.9)	6 (1.5)	0.01
Current refractory UTI[a]	10 (13.2)	9 (2.3)	<0.001
Corticosteroid use within 1 y	7 (9.2)	11 (2.8)	0.03

(Continues)

TABLE 1 (Continued)

Variable	ESBL+ (n = 76)	ESBL- (n = 390)	P value
Corticosteroid use within 90 d	5 (6.6)	9 (2.3)	NS
Corticosteroid use within 30 d	5 (6.6)	9 (2.3)	NS
Chemotherapy within 1 y	0 (0)	2 (0.5)	N/A
Chemotherapy within 90 d[c]	0 (0)	0 (0)	N/A
Chemotherapy within 30 d[c]	2 (2.6)	6 (1.5)	NS
Immunosuppressant[b] use within 1 y	1 (1.3)	0 (0)	N/A
Immunosuppressant[b] use within 90 d[c]	0 (0)	0 (0)	N/A
Immunosuppressant[b] use within 30 d	6 (7.9)	5 (1.3)	0.01

Age is presented as median. All other data are presented as n (%). Significant P values are represented numerically; nonsignificant P values, defined as >0.05, are noted with "NS."

[a]Current refractory UTI was defined as patients presenting to the ED with unresolved symptoms despite reported outpatient antimicrobial use. Outpatient antimicrobial use reported included fluoroquinolones, nitrofurantoin, trimethoprim/sulfamethoxazole, first- or second-generation cephalosporins, and beta-lactam/beta-lactamase inhibitors.

[b]Immunosuppressant use excluding corticosteroids and chemotherapy.

[c]Number of individuals with a single response in the overall the sample is <10. Variable was not included as a potential predictor in the external cross-validation model.

ESBLE, extended-spectrum beta-lactamase-producing enterobacteriaceae; GU, genitourinary; PICC, peripherally inserted central catheter; UTI, urinary tract infection.

TABLE 2 Patient disposition and antimicrobial therapy

Patient management	ESBL+ (n = 76)	ESBL- (n = 390)
Disposition		
Discharged	64 (84.2)	367 (94.1)
Admitted	12 (15.8)	22 (5.6)
Observation	0 (0)	1 (0.3)
Empiric antibiotic treatment		
Aztreonam	0 (0)	3 (0.8)
Beta-lactam/beta-lactamase inhibitor	5 (6.6)	4 (1)
First- or second-generation cephalosporin	10 (13.1)	46 (11.8)
Third-generation cephalosporin	33 (43.4)	178 (45.6)
Fourth-generation cephalosporin	0 (0)	0 (0)
Fluoroquinolone	14 (18.4)	58 (14.9)
Nitrofurantoin	12 (15.8)	91 (23.3)
Trimethoprim/sulfamethoxazole	3 (3.9)	12 (3.1)
Other	3 (3.9)	7 (1.8)
Antibiotic therapy modification at follow-up call*	30 (39.5)	25 (6.4)

All results presented as n (%). If not otherwise noted, there was no significant difference between the groups. A statistically significant difference was defined as P < 0.05.

*Odds ratio = 9.52, 95% confidence interval (8.91, 10.13), P < 0.001.

ESBL, extended-spectrum-beta-lactamase.

TABLE 3 Independent predictors of ESBLE UTI

Independent predictor	ESBL+ n(%)	ESBL- n(%)	OR	95% CI
IV antibiotics within 1 y	20 (26.3)	26 (6.7)	5.44	2.14-12.82
Any surgery within 90 d	11 (14.5)	8 (2.1)	6.44	1.49-27.82
Refractory UTI	10 (13.2)	9 (2.3)	8.50	1.98-36.56

CI, confidence interval; ESBLE, extended-spectrum beta-lactamase-producing enterobacteriaceae; OR, odds ratio; UTI, urinary tract infection.

TABLE 4 ESBLE UTI prediction score

Predictor score	Sensitivity (CI)	Specificity (CI)
1	11 (7.9-14.1)	55.4 (44.1-66.7)
2	85.1 (81.8-88.4)	20 (0-44.8)

CI, confidence interval; ESBLE, extended-spectrum beta-lactamase-producing enterobacteriaceae; UTI, urinary tract infection.

5 | DISCUSSION

In our study of 466 ED patients, IV antibiotic administration within 1 year, surgery within 90 days, and current refractory UTI were identified as independent risk factors for ESBLE UTI. Using an additive scoring system in patients diagnosed with UTI, 85.1% of patients with any 2 of these risk factors will grow an ESBL+ culture with a specificity of 20%. Compared to ESBL- patients, ESBL+ patients were significantly more likely to require antibiotic therapy modification. To our knowledge, our study is the first to endeavor to identify risk factors for ESBLE UTI in ED patients and develop an applicable predictor scoring system.

The independent risk factors for ESBLE UTIs identified in our study are consistent with some of those identified in previous literature. In a study in Thailand, ESBLE in ED UTIs were associated with previous use of antibiotics, previous ESBLE UTI, and current urinary catheter use.[3,16] Among hospitalized patients with community-acquired UTIs, indwelling urinary catheters, history of recurrent UTIs, or recent antimicrobial use were associated with ESBLE infection. In a study on elderly hospitalized patients, Artero et al identified recurrent UTIs and health care-associated UTIs (hospitalization within 3 months, antibiotic use within 3 months, or nursing home residence) as risk factors for ESBLE UTI. In non-hospitalized patients, diabetes mellitus, recent fluroquinolone use, recurrent UTI, hospital admission within 1 year, older age in males, bladder catheter use, and functional dependence were identified as possible risk factors for ESBLE UTI.[12,22] A risk factor of particular interest is previous antibiotic use. Our study, as well as all of the previously discussed studies, has identified either previous IV or oral antibiotic use as a risk factor for ESBLE UTI. This finding highlights the importance of antimicrobial stewardship in reducing the risk of ESBLE UTIs.

Interestingly, although identified in several previous studies, the presence of indwelling urinary catheter was not an independent predictor of ESBLE UTIs in our ED population. This may be because of the difference in population, that is, focus on ED patients, or overall low incidence of the risk factor in our study. Although presence of urinary catheters was included in our analysis, additional risk factors described in previous studies in ED and hospitalized patients were excluded from our cross-validated predictor model owing to very low incidence.

Our study is unique in its use of the identified predictors to develop and internally validate an ESBLE risk assessment tool for ED patients with UTI. Previous studies have developed scores such as an ESBL risk prediction score for bacteremia and a risk prediction score for multidrug-resistant organisms in ED UTI patients.[14] Using a cutoff of 2 points, we had a high sensitivity but low specificity for the identification of ESBLE UTI. Thus in a low prevalence setting (eg, 5% ESBLE UTI

prevalence), our predictor score test (2 points) would provide a high negative predictive value. Given the low prevalence of ESBLE UTI, further studies are needed to develop a risk score with higher specificity to better predict risk of ESBLE UTI. Further studies should also explore alternative outpatient oral antimicrobial options for patients identified to be high risk for ESBLE UTI, such as fosfomycin.[14] Keeping in mind the previously discussed limitations of our retrospective study, these results are hypothesis generating and would require further validation in future studies.

In summary, our retrospective case-control study identified previous IV antibiotic use within 1 year, any surgery within 90 days, and current refractory UTIs as independent predictors of ESBLE UTI in the ED. Our internally validated scoring system has a high sensitivity and low specificity in the identification of ESBLE UTI in ED patients, which can provide a high negative predictive value in a low disease prevalence setting. Further multicenter studies are required to externally validate our results for other health care settings and potentially elucidate additional risk factors for ESBLE UTI.

AUTHOR CONTRIBUTION

RS, NN, PB, POS, JM, TJK contributed to the conception and the design of the research. EZ and RS contributed to the data collection. PO, RS, NN, PB, JM contributed to the data analysis and interpretation. RS and EZ drafted the manuscript. All authors critically revised the article, read and approved the final article, and agree to be fully accountable for ensuring the integrity and accuracy of the work. RS takes responsibility for the paper as a whole.

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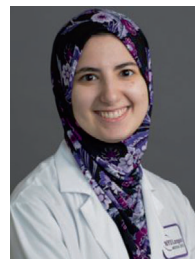
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