Minimizing time to optimal antimicrobial therapy for Enterobacteriaceae bloodstream infections:

A retrospective, hypothetical application of predictive scoring tools versus rapid diagnostics tests

Authors: Laura N. Cwengros, PharmD, Ryan P. Mynatt, PharmD, Tristan T. Timbrook, PharmD, MBA, Robert Mitchell, MT (ASCP), Hossein Salimnia, PhD, Paul Lephart, PhD, D (ABMM), Jason M. Pogue, PharmD

Affiliations:

1. Department of Pharmacy Services, CJW Medical Center, Richmond, Virginia, USA
2. Department of Pharmacy Services, University of Kentucky Healthcare, Lexington, Kentucky, USA
3. BioFire Diagnostics, Salt Lake City, UT, USA
4. Microbiology Division, Detroit Medical Center University Laboratories, and Wayne State University School of Medicine, Detroit, MI, USA
5. Clinical Microbiology Laboratory, University of Michigan, Ann Arbor, MI, USA
6. Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA

Corresponding Author:

Dr. Laura N. Cwengros, PharmD, BCIDP, Department of Pharmacy Services
Johnston-Willis Hospital, 1401 Johnston Willis Dr., Richmond, VA, 23235, USA
Office: 804-483-5106, Email: Laura.Cwengros@HCAHealthcare.com

Key points:
Verigene®, a rapid diagnostic test outperformed published scoring tools to predict ESBL producing Enterobacteriaceae bacteremia. Stewardship programs should strongly consider the adoption of rapid diagnostic tests to better optimize early therapies.

**Keywords:** Verigene, rapid diagnostics, ESBL, tool

**Background:** Bloodstream infections (BSIs) due to ceftriaxone (CRO) resistant Enterobacteriaceae are associated with delays in time to appropriate therapy and worse outcomes compared to infections due to susceptible isolates. However, treating all at-risk patients with empiric carbapenem therapy risks overexposure. Strategies are needed to appropriately balance these competing interests. The purpose of this study was to compare four methods for achieving this balance.

**Methods:** This was a retrospective hypothetical observational study of patients at the Detroit Medical Center with monomicrobial BSIs due to *E. coli, K. oxytoca, K. pneumoniae,* or *P. mirabilis.* This study compared the effectiveness of four methods to predict CRO resistance at the time of organism isolation. Three methods were based on applying published extended spectrum beta-lactamase (ESBL) scoring tools. The fourth method was based on the presence or absence of the CTX-M marker from Verigene®.

**Results:** 451 Enterobacteriaceae BSIs were included, 73 (16%) of which were CRO-resistant. Verigene® accurately predicted ceftriaxone susceptibility for 97% of isolates, compared to 70 – 81% using the scoring tools (p < 0.001). Verigene® was associated with fewer cases of treating with CRO when the isolate was CRO-resistant (15% versus 63-71% with scoring tools), and fewer cases of overtreatment with a carbapenem for CRO-susceptible strains (0.3% versus 10 – 12%).

**Conclusions:** Verigene® significantly outperformed published ESBL scoring tools for identifying CRO-resistant Enterobacteriaceae BSI. Institutions should validate scoring tools prior to implementation. Stewardship programs should consider adoption of rapid diagnostic tests to optimize early therapy.
Background:

Bloodstream infections (BSIs) are the seventh leading cause of death in the United States. With increasing rates of antimicrobial resistance, gram-negative BSIs are of particular concern. One of the most challenging resistance threats is the increasing frequency of ceftriaxone-resistance Enterobacteriaceae. Given the commonality of Enterobacteriaceae as a cause of BSIs, and the increasing frequency of resistance to first line therapies (i.e. ceftriaxone), impact on patients is substantial. Data have shown that BSIs due to extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, the most common mechanism of resistance to 3rd generation cephalosporins in Enterobacteriaceae, are associated with increased mortality, length of hospitalization, and healthcare costs, with a primary reason being significant delays in administration of appropriate antibiotics.

In many institutions, resistance to 3rd generation cephalosporins is not identified until final antimicrobial susceptibility tests (ASTs) return 48-96 hours after collection of blood cultures. This leads to significant delays in time to therapy modification and increases risk of negative outcomes. Conversely, widespread use of carbapenems as empiric therapy to ensure coverage of these resistant organisms is of concern, as carbapenem usage is a known risk factor for the emergence of carbapenem-resistant organisms. Therefore, strategies to more rapidly and accurately identify patients with third generation cephalosporin resistant (3GCR) Enterobacteriaceae are urgently needed in order to walk the tight rope between earlier appropriate therapy and overuse of carbapenems.

To aide in predicting patients with 3GCR Enterobacteriaceae, clinicians can utilize risk factors reported for ESBL including the presence of invasive devices, increased age, intensive care unit (ICU) stay, nursing home residence, and prior antimicrobial exposures. These risk factors can be utilized to create and ultimately implement a bedside prediction tool. If derived properly, bedside prediction tools could be of great value to the end-user allowing high probability of detecting an ESBL with only a few clinical variables. Ideally, variables included in the prediction tool would be easily retrievable from the electronic medical record (EMR) at the time of admission or suspicion of infection.
At the time of this study, two prediction scores had been published to assist providers in identifying those at risk for ESBLs. Augustine and colleagues developed a risk score which included three risk factors: recent outpatient genitourinary/gastrointestinal procedure, prior β-lactam or fluoroquinolone exposure, and prior infection/colonization with ESBL Enterobacteriaceae within the previous year. This scoring tool created weight based scores based on magnitude of risk with each factor, and after analysis of various scores, the authors recommended that patients with high risk of an ESBL BSI (prediction score of ≥ 3) or critically ill moderate risk patients (score of 1-2) should receive an empiric carbapenem. This cutoff threshold of 3 demonstrated an negative predictive value (NPV) of 97% and thus there was confidence it would not lead to undertreatment in many patients.7

Similarly, Lee and colleagues created a scoring tool for patients at risk for community-onset ESBL BSI.7 The authors demonstrated that nursing home residents, frequent and recent emergency department (ED) visits, recent antimicrobial exposure, and recent invasive procedures were all independent predictors. Each independent factor was equally assigned one-point and the authors recommended starting empiric carbapenem therapy with a score ≥ 2. This score had a NPV of 99% and thus the authors had confidence that it would not lead to undertreatment. An important limitation of both scoring tools is that they were derived in populations with low ESBL rates (5-6%). Given the infrequency of the event, the NPV would be expected to be high regardless of the performance of the test. Importantly, the positive predictive value (PPV) of the test was poor in both analyses ranging from 33-40%, suggesting a high likelihood of overtreatment with carbapenems with their application.6,7 Furthermore, the performance of these tests at an institution like ours that has ESBL rates approaching 20%, remains unclear.8

An alternative approach to scoring tools to more rapidly identify patients with resistant pathogens is using rapid diagnostic tests (RDTs). When paired with antimicrobial stewardship (ASP), RDTs have demonstrated reductions in mortality for patients with Gram-negative bacteremias. While multiple RDT platforms can rapidly determine organism identification to allow application of the aforementioned scores, Verigene® has the capability to identify the predominant ESBL resistance gene CTX-M. Verigene®’s performance to accurately predict ceftriaxone susceptibility in Enterobacteriaceae was recently assessed at both the Detroit Medical Center (DMC) and the University of Maryland Medical Center.8 Although the platform only detects one resistance gene for ESBL (blaCTX-M), the sensitivity, specificity, PPV and NPV were high in this analysis, suggesting that other mechanisms contribute only a minor proportion to 3GCR in these pathogens. Notably the PPV in this study was much higher (~95%), with similar NPV to the scoring tools.
These findings suggest that a treatment algorithm based on CTX-M status could appropriately identify patients who warrant carbapenem usage while limiting unnecessary overexposure.

At the time of this study, no analyses have either validated the scoring tools or a Verigene-based algorithm, or compared these methods in a head-to-head analysis. Therefore, the purpose of this study is to compare four different treatment algorithms for the management of Enterobacteriaceae BSI in a single cohort of patients.

Methods:

This was a retrospective observational study of adult patients within the DMC, an 8-hospital health system. Patients with Gram-negative bacteremia were identified from a microbiological database. Patients were eligible if they had a monomicrobial Enterobacteriaceae BSI from July 1, 2016 to July 31, 2017. For this analysis, only Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, or Proteus mirabilis BSIs were eligible as those are Enterobacteriaceae species detected by Verigene®’s Gram Negative-Blood Culture (GN-BC) panel. Although Enterobacter and Citrobacter spp. are also identified by Verigene®, it is standard practice at the DMC to avoid 3GC for the treatment of BSIs due to these pathogens regardless of susceptibility and therefore these pathogens were excluded. Patients were also excluded if carbapenemase genes were detected, as the purpose of this analysis was not to assess the application of these pathways for carbapenemase producing organisms. Additionally, only the first patient episode over the study period was eligible.

CLSI considers any E. coli, K. pneumoniae, K. oxytoca, or P. mirabilis with a minimum inhibitory concentration (MIC) ≥ 2 mcg/mL to ceftriaxone (CRO), ceftazidime, or aztreonam to be an ESBL. The DMC utilized BD Phoenix testing (Becton, Dickinson and Co., Sparks, MD) for susceptibility testing and at the time of the study had adopted these CLSI breakpoints. Therefore, for the purposes of this study, CRO-resistance or 3GCR and ESBL are used interchangeably.

This study assessed the appropriateness of four methods for determining whether to start either a carbapenem or ceftriaxone at the time of organism identification, defined as 24 hours after the blood culture was drawn, for treatment of a Gram-negative bacteremia. For purposes of the study, we assumed all blood cultures turned positive at 24 hours. Each patient was hypothetically managed and had treatment decisions based on the aforementioned algorithms by each of the four approaches: (1) Verigene®, based on presence or absence of the CTX-M resistance marker (2 & 3) two scores applied by the Augustine scoring tool’s different approaches and (4) a score applied by the Lee scoring tool.
For consistency in treatment, all patients were hypothetically started on ceftriaxone for Gram-negative coverage. For study purposes, time 0 represents the day blood cultures were drawn and initial ceftriaxone was started. The first decision point occurred at 24 hours assuming that at this time point either traditional microbiology would have identified a Gram-negative rod in the blood or Verigene® would have determined both organism identification and presence/absence of CTX-M. The decision to either continue ceftriaxone or escalate to a carbapenem occurred at this point in each of the four pathways (Figure 1). If CTX-M was identified with Verigene®, patients were hypothetically changed from ceftriaxone to a carbapenem. For the Augustine scoring tool, patients were hypothetically changed to a carbapenem if the ESBL prediction score was ≥ 3 or if a patient was critically ill with an ESBL score of 1-2 (defined as Augustine Approach 1). Additionally, this study also applied the Augustine scoring tool regardless of severity of illness, by hypothetically giving a carbapenem only if the ESBL-prediction score was ≥ 3 as this score was associated with the highest performance in their analysis (Augustine Approach 2). Similarly, for the Lee approach, in accordance with the authors’ recommendations, patients were treated with a carbapenem if the ESBL prediction score was ≥2. If any of these results were negative (CTX-M negative or scoring systems below threshold values) patients were "maintained" on ceftriaxone. Final antibiotic decisions were made at 72 hours when phenotypic antibiotic susceptibility from Phoenix BD became available and were based on actual patient isolates.

**Study outcomes:**

The sensitivity, specificity, PPV and NPV for predicting ceftriaxone susceptibility were assessed in the four approaches (where the “test” was the treatment approach and the “condition” was presence/absence of ceftriaxone resistance). Additionally, the number of patients that would have been inappropriately maintained on ceftriaxone therapy in the setting of ceftriaxone resistance and the number of patients unnecessarily escalated to a carbapenem in the setting of ceftriaxone susceptibility were assessed.

In order to gauge the impact following the different treatment pathways would have on total carbapenem usage the following procedure was used. For each patient the actual inpatient antimicrobial days of therapy for the BSI was determined. Then each decision tree as described above was applied to that patient to assess the number of carbapenem patient days per total treatment days that would have occurred had the algorithms been followed. For example, if a patient met the scoring criteria for escalation to a carbapenem, but ultimately would have been de-escalated back to ceftriaxone based on absence of ceftriaxone resistance and completed a 7 day course of IV antibiotics in the hospital, they would have been considered to have 2 carbapenem days (days 2 and 3 of therapy) out of 7 total BSI treatment days.
This process was then completed for every patient with each treatment algorithm and the results for each individual method were summed. The resultant number of carbapenem days was then normalized to 1000 inpatient BSI treatment days in order to compare total carbapenem exposures between application of the different pathways.

*Covariates collected*

Covariates collected from the electronic health record included demographics; comorbid conditions, presence of indwelling devices, microbiological and antimicrobial histories, components of the Pitt bacteremia score; ICU admission; physician diagnosis and source of infection; and other variables in previously published scoring tools.12

*Statistical analysis*

Chi-square tests were utilized to compare the accuracy of the various treatment pathways to predict ceftriaxone susceptibility. The performance of ESBL risk scores and Verigene® were compared to phenotypic testing using receiver-operating-characteristic (ROC) curve analysis. These analyses were performed in R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) using the pROC package.

*Results*

*Description of the cohort*

During the study period, 451 patients with Enterobacteriaceae BSI were included. Overall, the mean age was 65 ± 17 years, 242 (54%) were female, and 327 (73%) were African American. Common comorbidities included diabetes (191, 40%), chronic kidney disease (108, 24%), and chronic obstructive pulmonary disease (79, 18%). Eighty-four patients (17%) presented from a nursing home and 186 patients (41%) were hospitalized in the previous 90 days. Forty-eight (11%) patients had indwelling urinary catheters, and 47 patients (10%) had central venous catheters (Table 1).

Antibiotic exposure in the previous 4 weeks was observed in 86 (19%) patients, with 86 (19%) receiving at least one and 40 (9%) receiving ≥ 2 beta lactam or fluoroquinolone courses within the previous 90 days. Forty-two (9%) patients had a recent gastrointestinal/genitourinary tract procedure and 40 (9%) had an invasive procedure within the previous 4 weeks. Additionally, 74 (16%) had ≥ 3 ED visits within the
previous year, and 33 (7%) had infection or colonization with an ESBL producing organism within the previous year. The distribution of scores via the Augustine and Lee methods are displayed in Table 2.

The predominant organism was *E. coli* (287, 64%), followed by *K. pneumoniae* (112, 25%), and *P. mirabilis* (48, 11%). A total of 73 isolates (16%) were resistant to 3rd generation cephalosporins. Rates of resistance to third generation cephalosporins were 17% for *E. coli*, 17% for *K. pneumoniae*, 10% for *Proteus mirabilis*, and 25% for *K. oxytoca*.

Hypothetical escalation at 24 hours based on the four treatment pathways

CTX-M was detected in 63 isolates (14%) leading to escalation in those patients, while the remaining 388 patients (86%) remained on ceftriaxone. Using the scoring tool from Augustine, approach 1 led to escalation in 74 patients (16%), whereas approach 2 led to escalation in 61 (14%) of patients. Similarly, applying the Lee scoring tool led to escalation in 60 (14%) patients.

Accuracy of approaches (Table 3)

With regards to appropriately predicting CRO susceptibility, Verigene® correctly predicted ceftriaxone susceptibility results in 439 isolates (97%) and this was significantly higher than all score-based approaches: Augustine Approach 1 (358, 79%), Augustine Approach 2 (359, 80%), and Lee (364, 81%) (p < 0.001 for all comparisons). In the 378 ceftriaxone-susceptible isolates, unnecessary escalation to a carbapenem would have occurred in 1 patient utilizing the Verigene® approach, compared to 47 (12%), and 40 (11%) utilizing the two Augustine approaches and 37 (10%) utilizing the Lee method. Additionally, failure to appropriately escalate in patients with ceftriaxone-resistant isolates would have occurred in 11 of 73 (15%) resistant isolates with the Verigene® based algorithm. The rates of failure to escalate were higher with application of both the Augustine (n = 46, 63% approach 1; n = 52, 71% approach 2) and Lee (n = 50, 69%) methods.

The sensitivities, specificities, PPV and NPV of the various approaches are presented in table 3, while the area under the ROC curves are displayed in figure 2. Verigene® performed significantly better than any scoring tool with regards to each of these measures.

Total carbapenem consumption by treatment approach

The number of carbapenem days per 1000 BSI patient days for Verigene®, Lee, Augustine Approach 1, and 2 were similar at 136 days, 134 days, 142 days, and 134 days, respectively.
Discussion

The most important finding of this analysis is that while Verigene\textregistered performed very well in predicting ceftriaxone susceptibility in these isolates, both published ESBL scoring tools performed poorly. While the PPV of the scoring tools of were expectedly low (34 – 38% in this study, which was similar to the 33 – 40% values in their published analyses), the sensitivity and subsequent NPVs were unacceptably low. Roughly, two thirds of ceftriaxone resistant isolates would have been missed suggesting limited utility of these scores at our institution. These findings highlight the importance of site-specific validation of published scoring tools prior to implementation.

There are multiple possible explanations for the failure of these scoring tools in this analysis. The most important is local epidemiological differences between institutions. ESBL rates in target pathogens at the DMC are ~3-fold higher than either of the sites where these scores were developed. However, this increased rate would more be expected to impact the specificity than sensitivity, and thus the failure to detect roughly two thirds of ceftriaxone-resistant isolates was alarming. This is despite relatively similar patient populations between the current study and those from which the scores were derived. This was particularly true for the study by Augustine where demographics, healthcare exposures, and presence of indwelling catheter rates were similar. Conversely, all variables that were high predictors of ESBL in their model occurred more frequently in our patient population (recent GI/GU procedure 9.3 % vs. 5.4%; ≥ 2 prior courses of beta-lactams or fluoroquinolones 8.9% vs. 4.3%; and prior infection/colonization with ESBL producing organisms 7.3% vs. 1.6%). The high reliance on these infrequent events likely overstated their importance in predicting 3GC resistance (leading to the low specificity) and potentially “hid” the impact of other important factors (leading to the low sensitivity) in this population. The low incidence of ESBL at their institution likely exacerbated these issues.

With regards to the Lee study there were significant differences between the study populations with respect to multiple important components of the scoring tool, in addition to the low ESBL rate in their analysis. In the current analysis there were significantly higher numbers of nursing home patients (17% vs. 5%), recent invasive procedures (8.9% vs. 2.5%), and significantly less patients with “frequent ED visits” (16% vs. 30%). Therefore, the failure of this scoring tool to predict ESBLs in our population is not overly surprising. Similarly, a high reliance on infrequent events, could limit the reliability of a scoring tool in an external population.
Another interesting finding was that even though the Verigene® based algorithm would have led to 35-41 patients being placed on appropriate carbapenem therapy two days earlier it would not have led to an increase in overall carbapenem use in the population (136 carbapenem days/1000 BSI patient days compared to 134 – 142 carbapenem days/1000 BSI patient days). This is because the early appropriate usage of carbapenems in the Verigene® algorithm was offset by the early inappropriate usage directed by the scoring tools. Thus, the Verigene® based algorithm was successful in optimizing empiric activity, while limiting unnecessary use of carbapenems, and demonstrates the importance of rapid diagnostics for optimal stewardship practices.

There are limitations to this analysis that warrant comment. First, we excluded patients that had BSI due to Enterobacter spp., Citrobacter spp., and other “off panel” Enterobacteriaceae, which can be important causes of BSI. However, this was done purposely as we were assessing strategies to determine if ceftriaxone was appropriate or not for the management of infections based on various treatment algorithms, and at many institutions, including the DMC, ceftriaxone is not considered for the treatment of these pathogens. Additionally, the scoring tools assessed were developed on the same four pathogens included in this study and the distribution of these pathogens were similar to the present analysis. Nonetheless, these findings would not be applicable to any of these other pathogens or non-fermenting Gram-negative bacilli, where resistance mechanisms can be quite diverse.

Secondly, this was a hypothetical pathway implementation and therefore we are unable to assess either success with interventions based on these algorithms or their impact on outcomes. That said, these findings should help better implement these strategies in the future. Additionally, although we were unable to validate the scoring tools assessed in this study, they may still benefit institutions with similar ESBL rates and patient characteristics as the study populations from Augustine and Lee studies and warrant further exploration in that setting. Finally, this study was performed at an institution where CTX-M was known to predict ceftriaxone resistance with high degrees of accuracy. While a similar finding was demonstrated at the University of Maryland Medical Center, it would be important to validate these findings before implementing a Verigene® based pathway at another institution. While CTX-M is the predominant cause of 3GC resistance in these study pathogens in the United States, resistance can be seen due to other mechanisms, highlighting the importance of incorporating local epidemiology into any treatment paradigm.

In closing, this analysis demonstrated that Verigene® was highly accurate in predicting ceftriaxone susceptibility in Enterobacteriaceae BSI and that published ESBL scoring tools performed poorly.
Antimicrobial stewardship programs should incorporate rapid diagnostic tests into the management of Enterobacteriaceae BSIs wherever possible, however internal validation of pathways is critical.

Notes:

Potential conflicts of interest: T.T.T. has served as a consultant to BioFire & GenMark Diagnostics. J.M.P. is a consultant for Accelerate Diagnostics. All other authors report no potential conflicts of interest. No funding source was utilized for this research.

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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(6): 501-509.
2. Gupta V, Ye G, Olesky M, Lawrence K, Murray J, Yu K. National prevalence estimates for resistant Enterobacteriaceae and Acinetobacter species in hospitalized patients in the United States. Int J Inf Dis. 2019; 85: 203-11.
3. Peleg AY, Hooper DC. Hospital-acquired infections due to Gram-negative bacteria. N Eng J Med. 2010; 362(19): 1804-13.
4. Chopra T, Marchaim D, Johnson PC et al. Risk factors for bloodstream infection caused by extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae: A focus on antimicrobials including cefepime. Am J Infect Control. 2015; 43(7):719-23.
5. Heil EL, Johnson JK. Impact of CLSI breakpoint changes on microbiology laboratories and antimicrobial stewardship programs. J Clin Microbiol. 2016; 54(4): 840-4.
6. Augustine MR, Testerman TL, Justo JA et al. Clinical risk score for prediction of extended-spectrum β-lactamase-producing Enterobacteriaceae in bloodstream isolates. Infect Control Hosp Epidemiol. 2017; 38(3): 266-72.
7. Lee C, Chu F, Hsieh C et al. A simple scoring algorithm predicting extended-spectrum β-lactamase producers in adults with community-onset monomicrobial Enterobacteriaceae bacteremia: Matters of frequent emergency department users. Medicine. 2017; 96(16): e6648
8. Pogue JM, Heil EL, Lehart P et al. An antibiotic stewardship program blueprint for optimizing Verigene® BC-GN within an institution: A tale of two cities. Antimicrob Agents Chemother. 2018; 62(5): e02538-17.
9. Nanosphere, Inc. 2014. Verigene Gram-negative blood culture nucleic acid test (BC-GN) package insert 027-00039-01, rev B. Nanosphere Inc, Northbrook, IL.
10. CLSI. 2018. Performance standards for antimicrobial susceptibility testing, 28th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute, Wayne, PA.
11. BD Phoenix NMIC-500 [package insert], Sparks, MD, USA: BD Diagnostic Systems; 2018.
12. Paterson DL, Ko WC, Von Gottberg A et al. Antibiotic therapy for Klebsiella pneumoniae bacteremia: Implications of production of extended-spectrum β-lactamases. Clin Infect Dis. 2004; 39(1): 31-7.
13. Lewis JS 2nd, Herrera M, Wickes B, Patterson JE, Jorgenson JH. First report of the emergence of CTX-M-type extended-spectrum beta-lactamases (ESBLs) as the predominant ESBL isolated in a U.S. health care system. *Antimicrob Agents Chemother.* 2007; 51(11):4015-21.

Table 1. Baseline Characteristics

| Characteristics                                      | N = 451 |
|------------------------------------------------------|---------|
| Age*                                                 | 65 ± 17 |
| Female                                               | 242 (54)|
| Race                                                 |         |
| African American                                     | 327 (72.5)|
| White                                                | 81 (18) |
| Other                                                | 43 (9.5)|
| Admission Source                                     |         |
| Home                                                 | 334 (74)|
| Nursing home                                         | 86 (19) |
| Rehabilitation center                                | 12 (3) |
| Outside hospital                                     | 4 (1)  |
| Other                                                | 17 (4) |
| Comorbidities                                         |         |
| Hospitalization in last 90 days                      | 186 (41)|
| Indwelling urinary catheter                          | 48 (10.6)|
| Indwelling central venous device                     | 47 (10.4)|
| GI feeding tube                                       | 33 (7.3)|
| Congestive heart failure                             | 85 (18.8)|
| Dementia                                             | 57 (12.6)|
| COPD                                                 | 79 (17.5)|
| Chronic kidney disease                               | 108 (23.9)|
| Solid tumor                                           | 85 (18.8)|
| Cerebrovascular disease                              | 58 (12.9)|
| Liver disease                                         | 54 (12) |
| Diabetes mellitus                                     | 181 (40.1)|
| Charlson Comorbidity Index*                           | 2 ± 2   |
| Other relevant variables for ESBL scoring tools       |         |
| Recent GI/GU procedure within 30 days                 | 42 (9.3)|
| Invasive procedure in previous 4 weeks               | 40 (8.9)|
| Number of prior beta-lactam and/or fluoroquinolone courses in previous 90 days |         |
| 1                                                     | 84 (18.6)|
| ≥ 2                                                   | 40 (8.9) |
| Any antibiotic exposure in previous 4 weeks          | 86 (19.1)|
Infection or colonization with ESBL in previous year 33 (7.3)
≥ 3 ED visits within the previous year 74 (16.4)
Pitt bacteremia score ≥ 4 59 (13.1)

Unless otherwise noted, data are presented as N (%); *mean ± SD

Table 2. ESBL Score Distribution for Augustine and Lee scoring tools

| ESBL score Distribution (n = 451) | Augustine et.al No. (%) | Lee et.al. N (%) |
|-----------------------------------|-------------------------|-----------------|
| 0                                 | 291 (64.5)              | 240 (53.2)      |
| 1                                 | 86 (19.1)               | 151 (33.5)      |
| 2                                 | 13 (2.9)                | 47 (10.4)       |
| ≥ 3                               | 61 (13.5)               | 13 (2.8)        |

Threshold to treat with a carbapenem awaiting final susceptibilities: score ≥ 3 or if a patient was critically ill with an ESBL score of 1-2 (Augustine Approach 1); score ≥ 3 (Augustine Approach 2); score ≥2 (Lee)

Table 3. Comparative accuracy of the various methods

| N = 451 | Cutoff | Appropriately predicted ceftriaxone-susceptibility | Over treatment N = 378 | Under treatment N = 73 | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value |
|---------|--------|---------------------------------------------------|------------------------|------------------------|-------------|-------------|---------------------------|---------------------------|
| Verigene CTX-M | 439 (97.3) | 1 (0.3) | 11 (15.1) | 85% | 99.7% | 98% | 97% |
| Lee 2 | 364 (80.7) | 37 (9.8) | 50 (68.5) | 32% | 90% | 38% | 87% |
| Augustine Approach 1 | 358 (79.4) | 47 (12.4) | 46 (63) | 37% | 88% | 36% | 88% |
| Augustine Approach 2 | 359 (79.6) | 40 (10.6) | 52 (71.2) | 29% | 89% | 34% | 87% |

Unless otherwise noted, data are presented as N (%); Over treatment = algorithm escalated patient to an empiric carbapenem on day 1 (final susceptibility = CRO susceptible); Under treatment = algorithm continued ceftriaxone on day 1 (final susceptibility = CRO resistant)
Figure 1: Hypothetical Treatment Pathways

Threshold for giving carbapenem at time 24 include the following: Verigene = CTX-M gene detected; Augustine 1 = score of ≥3 or score ≥1 in critically ill; Augustine 2 = score ≥3; Lee = score ≥2. (S) = susceptible; (R) = resistant; CRO = ceftriaxone; CARB = carbapenem
Figure 2: ROC curves

| Method | AUC     | 95% confidence interval |
|--------|---------|-------------------------|
| Verigene | 0.923   | 0.882 – 0.965           |
| Augustine | 0.711   | 0.649 – 0.774           |
| Lee     | 0.687   | 0.622 – 0.751           |