

# Efficacy of Noncarbapenem $\beta$ -Lactams Compared to Carbapenems for Extended-Spectrum $\beta$ -Lactamase–Producing Enterobacterales Urinary Tract Infections

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**Background.** Extended-spectrum  $\beta$ -lactamase (ESBL)–producing Enterobacterales are frequent causes of urinary tract infections (UTIs). Severe infections caused by ESBL Enterobacterales are often treated with carbapenems, but optimal treatment for less severe infections such as UTIs is unclear.

**Methods.** This retrospective cohort study included patients admitted to 4 hospitals in an academic healthcare system with an ESBL UTI treated with either a noncarbapenem  $\beta$ -lactam (NCBL) or a carbapenem for at least 48 hours from 1 April 2014 to 30 April 2018. Those who received an NCBL were compared to those receiving a carbapenem, with a primary outcome of hospital length of stay (LOS) and secondary outcomes of clinical and microbiological response, days until transition to oral therapy, rate of relapsed infection, and rate of secondary infections with a multidrug-resistant organism.

**Results.** Characteristics were similar among patients who received carbapenems ( $n = 321$ ) and NCBLs ( $n = 171$ ). There was no difference in LOS for the NCBL group compared to the carbapenem group (13 days vs 15 days,  $P = .66$ ). The NCBL group had higher rates of microbiologic eradication (98% vs 92%,  $P = .002$ ), shorter time to transition to oral therapy (5 days vs 9 days,  $P < .001$ ), shorter overall durations of therapy (7 days vs 10 days,  $P < .001$ ), and lower rates of relapsed infections (5% vs 42%,  $P = .0003$ ).

**Conclusions.** Patients treated with NCBLs had similar LOS, higher rates of culture clearance, and shorter durations of antibiotic therapy compared to patients treated with carbapenems, suggesting that treatment for ESBL UTIs should not be selected solely based on phenotypic resistance.

**Keywords.** antimicrobial resistance; antimicrobial stewardship; ESBL; extended-spectrum  $\beta$ -lactamase; urinary tract infection.

Extended-spectrum  $\beta$ -lactamase (ESBL)–producing Enterobacterales species are among the most frequently encountered antimicrobial-resistant organisms, but ideal treatment remains unclear, particularly for urinary tract infections (UTIs) [1]. Due to resistance to many cephalosporin and penicillin antibiotics, the treatment of choice for ESBL-producing Enterobacterales is often a carbapenem. However, increased use of carbapenems may be associated with both increased cost and the emergence of carbapenem-resistant Enterobacterales (CRE) [2]. To slow the growing resistance to carbapenems, safe and effective carbapenem-sparing treatment regimens are being evaluated.

According to the Centers for Disease Control and Prevention's 2019 Antimicrobial Resistance Threat Report, approximately 197 400 ESBL-producing Enterobacterales isolates are identified each year in the United States, which is an increase from approximately 131 900 in 2013 [2]. ESBL-producing organisms include *Escherichia coli*, *Klebsiella* species (spp), *Enterobacter* spp, *Proteus* spp, *Serratia* spp, and *Citrobacter* spp that contain genetic resistance to oxyimino-cephalosporins and penicillins [3, 4]. While many genetic mutations can culminate in ESBL production, the primary genotypes seen in clinical practice are CTX-M and the TEM and SHV families [3–6]. However, genotypic testing can be costly and may not be routinely utilized at all institutions for diagnostic practice. As a result, determination of the presence of ESBL production is often done by interpretation of phenotypic culture and sensitivity data, with in vitro resistance to ceftriaxone frequently used for identification. When this phenotypic pattern is seen, these organisms are often suspected to have in vivo resistance to other cephalosporins such as ceftazidime and cefepime, in addition to broad-spectrum  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination antibiotics such as piperacillin-tazobactam [7]. The Infectious Diseases Society of America (IDSA) practice guideline for the treatment of pyelonephritis and complicated UTIs

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caused by ESBL-producing Enterobacterales therefore recommends use of carbapenems, fluoroquinolones, or trimethoprim-sulfamethoxazole [1].

To date, there have been few studies investigating the use of carbapenem-sparing antibiotic regimens [8]. A systematic review did find that oral antibiotics for the treatment of UTIs caused by ESBL-producing organisms may serve to reduce length of hospital stay and spare carbapenem use without a negative impact on clinical outcomes [9], but the data have been less clear for patients requiring intravenous therapy. Harris et al's MERINO trial evaluated the difference in mortality in patients treated with piperacillin-tazobactam vs meropenem for *E coli* or *Klebsiella pneumoniae* bloodstream infections with resistance to ceftriaxone, and the investigators stopped the trial early due to a futility analysis favoring meropenem. However, the authors noted that mortality was much lower in patients with a urinary source, and so piperacillin-tazobactam might still be a suitable option for patients with UTIs caused by ESBL-producing organisms [10]. The IDSA guidelines therefore state that patients with cystitis who are empirically treated with piperacillin-tazobactam or cefepime and then are later determined to be infected with an ESBL-producing organism may continue on their empiric regimen if they demonstrate clinical improvement [1].

This recommendation is supported by the "90-60 rule" of antimicrobial susceptibility testing, which states that when treating a susceptible isolate appropriately, clinical response is achieved approximately 90% of the time, but when treating a resistant isolate with ineffective antimicrobials based on susceptibilities, clinical response is still achieved approximately 60% of the time [11]. This phenomenon may be due to overcalling resistance with set microbiological minimum inhibitory concentrations (MICs) or to a difference between in vitro and in vivo antimicrobial activity [11]. Clinical response to antimicrobials reported as resistant may be even more common in patients with ESBL UTIs, given the concentration of  $\beta$ -lactam antibiotics in the urine [12, 13]. We therefore decided to retrospectively evaluate outcomes of patients with ESBL UTIs treated with a noncarbapenem  $\beta$ -lactam (NCBL) vs a carbapenem, to explore whether NCBLs might be a reasonable alternative in this selected population.

## METHODS

We evaluated a retrospective cohort of hospitalized adult patients admitted to 4 hospitals in an academic healthcare system who were diagnosed with a UTI between 1 April 2014 and 30 April 2018. Patients were included for the study if they were at least 18 years of age, had a diagnosis of a UTI in the medical record as determined by physician documentation, had a positive urine culture with an ESBL-producing organism (defined as phenotypic resistance to ceftriaxone), and were treated with a carbapenem or an NCBL for at least 48 hours. Patients were

excluded if they were <18 years of age, pregnant, receiving antimicrobial prophylaxis, had an infection with the same organism at another site other than blood, or received fosfomycin at any point during hospitalization.

Patients were categorized as being treated with an NCBL (including ceftriaxone, cefepime, and piperacillin-tazobactam) or a carbapenem (meropenem, ertapenem, or doripenem) (Supplementary Table 1).

The primary outcome was hospital length of stay (LOS) in days. Secondary outcomes included clinical response to therapy (defined as positive if there was documented improvement in symptoms, negative if there was documented clinical worsening or change in therapy due to lack of therapeutic response, or uncertain if there were no comments on resolution of symptoms); microbiologic eradication (defined as positive if repeat urine culture was negative, negative if repeat urine culture was positive, and uncertain if no repeat urine cultures were collected); in-hospital mortality; 30-day readmission rate; days to transition from intravenous to oral therapy; total days of therapy; rate of *Clostridioides difficile* infection within 8 weeks of treatment; rate of relapsed infection (defined as recurrence of UTI with the same pathogen) within 30 days; rate of new infection with a new multidrug-resistant organism (MDRO) at a site other than urine (defined as resistance to at least 1 agent from 3 different classes of antibiotics); and rate of new infection with a carbapenem-resistant organism at any site within 30 days.

Patient demographic data (including age, sex, and weight) and 30-day readmission rates were extracted from the electronic medical record. Microbiologic culture data, medication administration documentation, and clinical outcomes data (eg, subjective reports of symptomatic improvement) were collected through a manual review of patient charts.

A subgroup analysis was performed comparing NCBLs to carbapenems for complicated UTIs. Patients were considered to have a complicated UTI if they had a documented structural abnormality, urinary obstruction, male sex, diabetes as determined by *International Classification of Diseases, Tenth Revision* code, immunosuppression (defined as current administration of cytotoxic chemotherapy, anti-tumor necrosis factor biological agents, or other immunosuppressive agents including use of 30 mg/day of prednisone or an equivalent; an absolute neutrophil count <500 cells/ $\mu$ L; presence of a solid tumor or hematologic malignancy; or human immunodeficiency virus/AIDS with a CD4 count of <200 cells/mL), presence of a urinary catheter, or diagnosis of pyelonephritis.

During the study period, there were no changes in laboratory procedures for reporting ceftriaxone susceptibilities or ESBL identification or confirmation with genetic testing. Only susceptibility interpretations were published in the patient's medical records. MICs were only reported if requested by the treating physician. Isolates with ceftriaxone resistance were presumed to be ESBL producing. Susceptibility interpretations for

other  $\beta$ -lactam antibiotics were not changed based on the presence of ceftriaxone resistance.

Patients receiving an NCBL antibiotic and those receiving a carbapenem were compared using  $\chi^2$  or Fisher exact tests for categorical variables and Student *t* tests for continuous variables. In addition, multivariable regression models were constructed to determine which patient factors were associated with an increased risk of mortality, relapsed infection, and microbiological eradication. Treatment with a carbapenem, the presence of a urinary catheter, and all other risk factors with  $P < .05$  in univariable analysis were included in the multivariable modeling. Additionally, generalized linear regression models with LOS as an outcome (excluding patients with malignancy as a factor known to prolong hospitalization, as well as patients with a LOS >100 days) were constructed using an inverse Gaussian distribution assumption.

## RESULTS

Among 1408 patients with a documented UTI caused by an ESBL-producing organism, 492 (35%) were included for analysis. Nine hundred sixteen patients were excluded from analysis: 11 pediatric patients, 391 who were treated with antibiotics

for <48 hours, 331 who received nonqualifying antibiotics, 60 who had confirmed coinfections, 119 who had polymicrobial UTIs, and 4 who were on antimicrobial prophylaxis prior to admission. Of the 492 patients included, 171 (35%) were treated with an NCBL and 321 (65%) were treated with a carbapenem (Table 1). The median age of patients in the study was 70 years (interquartile range, 56–81 years) and most patients were female (70%). The presence of concurrent bacteremia was significantly higher in the carbapenem group than in the NCBL group (11% vs 2.3%,  $P = .0004$ ).

There was no difference in mean hospital LOS between the 2 groups (13 days for the NCBL group vs 15 days in the carbapenem group,  $P = .66$ ). The NCBL group had a significantly shorter time to transition to oral therapy (5 days vs 9 days,  $P < .0001$ ) and a shorter total duration of therapy (7 days vs 10 days,  $P < .0001$ ). Fifty-three patients (31%) in the NCBL group and 144 patients (45%) in the carbapenem group had repeat urine cultures collected; among those patients, the NCBL group had a higher rate of microbiologic eradication (98% vs 92%,  $P = .0016$ ) and a lower rate of relapsed infections within 30 days (3% vs 13%,  $P = .0003$ ). There was no difference in the rate of positive clinical response (97% vs 96%,  $P = .28$ ), in-hospital mortality (4% vs 4%,  $P = .85$ ), or rates of *C difficile* infection in

**Table 1. Characteristics of Patients With a Urinary Tract Infection Treated With a Carbapenem Compared to Those Treated With a Noncarbapenem  $\beta$ -Lactam**

Characteristic	Carbapenem (n = 321)	NCBL (n = 171)	P Value
Patient demographics and clinical features			
Age, y, median (IQR)	69 (56–81)	72 (59–81)	.87
Male sex	111 (35)	50 (29)	.35
Weight, kg, median (IQR)	76 (64–94)	70 (64–90)	.14
Complicated UTI	244 (76)	118 (69)	.37
Bacteremia	35 (11)	4 (2.3)	.0004
Causative organism			
<i>Escherichia coli</i>	240 (74.8)	86 (50.3)	<.001
<i>Klebsiella pneumoniae</i>	54 (16.9)	34 (19.9)	.40
<i>Klebsiella oxytoca</i>	9 (2.8)	5 (2.9)	.94
<i>Enterobacter cloacae</i>	10 (3.1)	22 (12.9)	<.001
Other	8 (2.5)	24 (14)	<.001
Hospitalization outcomes			
Hospital LOS, d, median (IQR)	15 (5–13)	13 (4–12)	.66
Positive clinical response <sup>a</sup>	308 (96)	166 (97)	.28
In-hospital mortality	13 (4)	7 (4)	.84
Rates of CDI	19 (6)	7 (4)	.36
Secondary MDR within 30 d	29 (9)	9 (5)	.13
Secondary CRE within 30 d	2 (0.6)	0 (0)	.54
Microbiologic eradication <sup>b</sup>	295 (92)	168 (98)	.0016
Days to transition to oral therapy, mean (SD)	9 (4)	5 (3)	<.0001
Days of therapy, mean (SD)	10 (4)	7 (3)	<.0001
Relapsed infection within 30 d	42 (13)	5 (3)	.0003

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CDI, *Clostridioides difficile* infection; CRE, carbapenem-resistant Enterobacterales; IQR, interquartile range; LOS, length of stay; MDR, multidrug resistant; NCBL, noncarbapenem  $\beta$ -lactam; SD, standard deviation; UTI, urinary tract infection.

<sup>a</sup>Includes patients with documented improvement and patients without comments on improvement.

<sup>b</sup>Includes patients with documented eradication and assumed eradication due to lack of repeat culture.

**Table 2. Characteristics of Patients With a Complicated Urinary Tract Infection Treated With a Carbapenem Compared to Those Treated With a Noncarbapenem  $\beta$ -Lactam**

Hospitalization Outcome	Carbapenem (n = 244)	NCBL (n = 118)	P Value
Hospital LOS, d, median (IQR)	18.3 (6–14)	13.9 (4–12)	.59
Positive clinical response <sup>a</sup>	232 (95)	114 (97)	.46
In-hospital mortality	12 (5)	6 (5)	.97
Rates of CDI	18 (8)	6 (5)	.31
Secondary MDR within 30 d	27 (11)	6 (5)	.07
Secondary CRE within 30 d	1 (0.8)	0 (0)	1
Microbiologic eradication <sup>b</sup>	222 (91)	115 (98)	.005
Days to transition to oral therapy, mean (SD)	10 (4)	5 (3)	<.0001
Days of therapy, mean (SD)	10 (4)	8 (3)	<.0001
Relapsed infection within 30 d	37 (15)	4 (3)	.0009

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CDI, *Clostridioides difficile* infection; CRE, carbapenem-resistant Enterobacterales; IQR, interquartile range; LOS, length of stay; MDR, multidrug resistant; NCBL, noncarbapenem  $\beta$ -lactam; SD, standard deviation.

<sup>a</sup>Includes patients with documented improvement and patients without comments on improvement.

<sup>b</sup>Includes patients with documented eradication and assumed eradication due to lack of repeat culture.

the following 8 weeks (4% vs 6%,  $P = .36$ ) for patients receiving NCBLs vs carbapenems, respectively. There were also no differences in rates of secondary infections with MDROs (5% vs 9%,  $P = .14$ ) or CRE (0% vs 0.6%,  $P = .55$ ) (Table 1).

In a subgroup analysis of patients with a complicated UTI, the same differences in microbiologic eradication (98% vs 91%,  $P < .005$ ), time to transition to oral therapy (5 days vs 10 days,  $P < .0001$ ), duration of therapy (8 days vs 10 days,  $P < .0001$ ), and rates of relapsed infection within 30 days (3% vs 15%,  $P = .0009$ ) persisted, again favoring the NCBL group (Table 2).

Logistic regression models demonstrated that carbapenem therapy was not associated with mortality or a need for hospice care (odds ratio [OR], 0.99;  $P = .63$ ; Table 3). Carbapenem antibiotics were not associated with increased LOS in multivariable linear regression modeling that excluded patients with malignancy and LOS  $\geq 100$  days (OR, 0.99;  $P = .23$ ; Table 4).

## DISCUSSION

In this review of 492 patients with UTIs caused by ESBL-producing organisms, those treated with NCBLs had similar hospital LOS but had shorter times to transition to oral therapy

and shorter durations of therapy compared to those patients treated with carbapenems, with no difference in clinical outcomes. These findings persisted when evaluating the subset of patients with complicated UTIs.

The rates of treatment success and microbiologic eradication seen in our NCBL group are different than what was seen overall in the MERINO trial [10], although they support the subgroup analysis findings in which patients with UTIs had lower mortality. We suspect that the excellent urinary penetration of intravenous  $\beta$ -lactam antibiotics is a significant contributor to the outcomes seen with NCBL use in our study [12]. The urinary penetration of these antibiotics likely leads to sufficient concentrations to overcome common enzymatic mechanisms of resistance, making UTIs a unique infection where carbapenems may not be universally necessary for ESBL infections [13]. This is supported by several recent retrospective studies demonstrating similar outcomes with piperacillin-tazobactam and carbapenems for the treatment of ESBL UTIs including pyelonephritis [14–16]. Additionally, a small prospective randomized trial found no difference in clinical or microbiologic outcomes when comparing piperacillin-tazobactam to ertapenem for the treatment of UTIs caused by ESBL-producing organisms. They did see inferiority of cefepime, but

**Table 3. Patient Factors Associated With Hospice Admission or Death**

Variable	OR (P value)
Bacteremia	0.90 (0.03)
Age	1.00 (0.07)
Diabetes	0.94 (0.05)
Antineoplastic	1.07 (0.03)
Catheter	1.10 (<0.01)
Carbapenem	0.99 (0.63)
Model statistics	
AIC value	261.85
$R^2$ value	0.05

Abbreviation: AIC, Akaike information criterion.

**Table 4. Patient Factors Associated With Hospital Length of Stay**

Variable	OR (P value)
Age	1.00 (<0.01)
Weight	1.00 (<0.01)
Antineoplastics	0.97 (<0.01)
Diabetes	1.02 (0.03)
Carbapenem	0.99 (0.23)
Model statistics	
AIC value	2630.6
$R^2$ value	0.11

Abbreviation: AIC, Akaike information criterion.

the significance of that finding is difficult to interpret given the potential for underdosing cefepime at 1 g twice daily [17].

While other observational trials have shown inferiority of NCBLs to carbapenems, these results have primarily been attributed to a high inoculum of bacteria and the severity of patient illness [18]. Many of these studies also either did not identify the site(s) of infection or did not stratify results based on sites of infection [19–29]. It is therefore possible that patients with UTIs have a lower bacterial inoculum and/or a decreased severity of illness, which may contribute to the results seen in our study in addition to the high levels of  $\beta$ -lactam penetration into the urine.

Another factor that may have contributed to our positive outcomes in patients treated with NCBLs is type of  $\beta$ -lactamase. The cefotaxime-M (CTX-M)  $\beta$ -lactamases are among the most prevalent ESBL enzymes worldwide, and they usually have increased susceptibility to cefepime and ceftazidime relative to ceftriaxone and are readily inhibited by tazobactam [30]. We were unable to obtain retrospective genotypic results, but if a high proportion of our isolates were CTX-M  $\beta$ -lactamases, that could contribute to comparable success rates for patients treated with cefepime, ceftazidime, and piperacillin-tazobactam and those treated with meropenem.

In addition to lack of genotype data, this study had several other limitations primarily related to its retrospective design. Though the results of this study are hypothesis-generating and consistent with prior data, due to the retrospective nature, causality cannot be attributed to the use of NCBLs for shorter durations of therapy, higher rates of eradication, and lower rates of relapsed infection. Repeat urine cultures are not standard of care for UTI treatment, and so it is possible that the presence of repeat urine culture results for some patients indicated a lack of improvement or concern for a new infectious process. Clinical outcomes were difficult to obtain on retrospective chart review due to poor documentation of symptomatic improvement. Additionally, while we were able to classify patients as complicated or uncomplicated based on complicating factors, reliance on documentation of symptoms prevented stratification based on pyelonephritis vs cystitis. Similarly, we were unable to adequately stratify patients based on presenting severity of illness. Given the higher percentage of bacteremic patients in the carbapenem group and possible differences in severity of illness, prolonged hospitalizations, longer durations of therapy, and increased time to transition to oral therapy may reflect a propensity for providers to select a broader-spectrum antibiotic in patients with increased severity of illness and/or other confounding medical issues rather than the effect of the agent chosen for treatment. The increased incidence of bacteremia in the carbapenem group supports a consideration that these patients may have had increased severity of illness, although differences between the carbapenem and NCBL groups persisted with bacteremic patients excluded. Due to an insufficient

number of patients with bacteremia in the NCBL arm, we were unable to perform a subgroup analysis of patients with bacteremia secondary to a urinary source.

## CONCLUSIONS

Our results are encouraging that NCBLs may provide an alternative to carbapenems for treatment of UTIs, given no increased risk of mortality and some benefits with respect to antibiotic duration seen. The relatively low inoculum of bacteria thought to be present in UTIs and excellent urinary penetration of  $\beta$ -lactam antibiotics make NCBLs an attractive, carbapenem-sparing therapy option for patients with a UTI caused by an ESBL-producing organism. Given that cultures and susceptibility data are usually available within the first 48–72 hours of a patient's treatment, it may be reasonable to select targeted antimicrobials based on clinical status in addition to phenotypic resistance patterns. Future studies could include a larger cohort of patients with bacteremia secondary to UTI to establish the safety and efficacy of NCBLs compared to carbapenems for the treatment of bacteremia with a urinary source. Additionally, an analysis of non- $\beta$ -lactam antibiotics such as trimethoprim-sulfamethoxazole, fluoroquinolones, or fosfomycin compared to NCBL or carbapenems would help guide treatment in patients with a UTI caused by an ESBL-producing organism.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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**Patient consent.** The design of the work has been approved by the Emory University Institutional Review Board. Given that this was a retrospective, cohort study, patient consent was not required.

**Potential conflicts of interest.** All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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