Efficacy of Ertapenem for Treatment of Bloodstream Infections Caused by Extended-Spectrum- β -Lactamase-Producing *Enterobacteriaceae*

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Ertapenem is active against extended-spectrum- β -lactamase (ESBL)-producing *Enterobacteriaceae* organisms but inactive against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Due to a lack of therapeutic data for ertapenem in the treatment of ESBL bloodstream infections (BSIs), group 2 carbapenems (e.g., imipenem or meropenem) are often preferred for treatment of ESBL-producing *Enterobacteriaceae*, although their antipseudomonal activity is unnecessary. From 2005 to 2010, 261 patients with ESBL BSIs were analyzed. Outcomes were equivalent between patients treated with ertapenem and those treated with group 2 carbapenems (mortality rates of 6% and 18%, respectively; $P = 0.18$).

Extended-spectrum- β -lactamase (ESBL)-producing *Enterobacteriaceae* organisms are recognized as an imminent threat to public health (7, 26). No prospective, randomized, controlled trials have been conducted analyzing the preferred therapeutic management of ESBL-producing *Enterobacteriaceae* infections. Few small retrospective trials have demonstrated the relative superiority of carbapenems over other agents (4, 8, 12, 14, 17, 19, 21, 24, 31). The carbapenems that were studied were group 2 carbapenems (e.g., imipenem and meropenem). Ertapenem is a group 1 carbapenem with no appreciable activity versus *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (13). Unfortunately, there are limited data pertaining to the efficacy of ertapenem for the treatment of serious invasive infections, such as bloodstream infections (BSIs), that are due to ESBL-producing *Enterobacteriaceae* (2, 3, 6, 10, 13, 22, 23, 27–30). Due to a lack of data, many clinicians rely on group 2 carbapenems for treatment of severe ESBL infections. A recent, commonly cited expert opinion review article did not even mention ertapenem as an option for the treatment of BSIs due to ESBL-producing *Enterobacteriaceae* (25). This study aimed to compare the efficacies of group 1 carbapenems and group 2 carbapenems for the treatment of BSIs due to ESBL-producing *Enterobacteriaceae*.

A retrospective cohort study from 1 January 2005 to 30 June 2010 pertaining to outcomes of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* BSIs was conducted at the Detroit Medical Center (DMC) health system after institutional review board approvals. Only unique adult (>18 years old) patient episodes were included. BSIs were defined according to CDC and systemic inflammatory response syndrome (SIRS) criteria (11, 15). Polymicrobial infectious episodes were excluded. The time to initiation of appropriate therapy was captured in hours. Empirical regimens (antimicrobials administered from 48 h before to 71 h after the culture) and consolidative regimens (antimicrobials administered 72 h to 14 days following the culture) were reviewed. Only drugs for which ≥ 2 doses were administered were included as treatment agents. Outcomes captured included in-hospital and 3-month mortality, length of hospital

stay (LOS), deterioration in functional status (18), discharge to a long-term care facility (LTCF) after being admitted from home, additional hospitalization in the 6 months following discharge, and additional isolations of the same organism in the 3 months following the culture date (i.e., “bacteriologic failures”). Bacteria were identified to the species level, and susceptibilities to predefined antimicrobials were determined based on an automated broth microdilution system (Micro-Scan; Siemens AG, Germany) and in accordance with the CLSI criteria (9). For representative isolates, a positive ESBL test from the automated system was confirmed with disc diffusion tests (9). All analyses were performed using IBM SPSS 19 (2011). Logistic regression was used for multivariate analyses. Variables chosen for the model were based on clinical importance and the results of bivariate analyses between relevant groups (variables with a P value of ≤ 0.05). Variables with a P value of ≤ 0.05 were included in the final model and were adjusted for confounds. A propensity score analysis was conducted to establish the likelihood of receiving ertapenem and incorporated into outcome models.

The study cohort included 261 unique patients with BSIs due to ESBL-producing *Enterobacteriaceae* (Table 1). The majority of patients were elderly (53.6%), and 71% had a permanent device present for at least 48 h prior to ESBL-producing *Enterobacteriaceae* isolation. Most BSIs were from a urinary source ($n = 108$ [41.4%]), and 51 (19.5%) were primary BSIs. Rates of resistance to other antimicrobial agents were high. No resistance to group 2 carbapenems was noted, but two cases (9.5%) were resistant to

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TABLE 1 Characteristics of patients with bloodstream infections due to ESBL-producing *Enterobacteriaceae*^a

Parameter and characteristic	Value (%) ^b
Demographic information	
Age (yr) (mean ± SD)	65.5 ± 16.1
Elderly (≥65 years)	140 (53.6)
Female	124 (47.5)
African American	202 (78.6)
Source of bloodstream infection	
Central line associated	52 (19.9)
Urinary tract infection	108 (41.4)
Pneumonia	33 (12.6)
Intra-abdominal	24 (9.2)
Skin and soft-tissues, surgical sites, joints, and bones	31 (11.9)
Infection strain	
<i>Klebsiella pneumoniae</i>	128 (49)
<i>Escherichia coli</i>	133 (51)
Median MIC (IQR)	
Ertapenem	0.12 (0.06–0.5)
Drug resistance	
Ertapenem	2 (9.5)
Colistin	0 (0)
Tigecycline	0 (0)
Cefepime	252 (96.6)
Gentamicin	167 (64)
Tobramycin	207 (79.3)
Ciprofloxacin	203 (79.3)
TMP-SMX	165 (65.3)
Status at admission	
Dependent functional status	161 (61.7)
Rapidly fatal McCabe score	60 (23.0)
Diabetes mellitus	129 (49.4)
Chronic renal disease	65 (24.9)
Pulmonary disease	70 (26.8)
Congestive heart failure	101 (38.7)
Neurologic disease	84 (32.2)
Dementia	70 (26.8)
Malignancy	56 (21.5)
AIDS	4 (1.5)
Median Charlson's weighted index comorbidity score (range)	4 (0–12)
Median Charlson's combined condition score (range)	6 (0–17)
Charlson's 10-year survival probability (%) and median (range)	2 (0–98)
Major immunosuppressive state	55 (21.1)
Exposure to health care setting	
Admitted from LTCF	141 (54.0)
Regular visits to hemodialysis unit	65 (24.9)
ICU stay 3 months prior to ESBL isolation	120 (46)
Severity of illness indices at time of ESBL isolation	
Impaired consciousness	163 (62.5)
Severe sepsis/septic shock/multiorgan failure	80 (30.8)
Antimicrobial therapy	
Median time to effective therapy (h) (IQR)	52 (24–90)

TABLE 1 (Continued)

Parameter and characteristic	Value (%) ^b
Empirical therapy	
Penicillins ^c	42 (16.1)
Cephalosporins	157 (60.2)
Monobactam	14 (5.4)
Ertapenem	28 (12.6)
Group 2 carbapenems	106 (42.5)
Fluoroquinolones	27 (10.3)
Glycopeptides	122 (46.7)
Tetracyclines	18 (6.9)
Polymyxins	5 (1.9)
Aminoglycosides	41 (15.8)
TMP-SMX	8 (3.1)
Daptomycin	7 (2.7)
Linezolid	14 (5.4)
Macrolides	9 (3.4)
Clindamycin	8 (3.1)
Metronidazole	40 (15.4)
Rifampin	4 (1.5)
Main therapy	
Piperacillin-tazobactam	11 (4.2)
Cephalosporins	29 (11.2)
Cefepime	13 (5)
Ertapenem	72 (27.8)
Group 2 carbapenems	132 (51)
Fluoroquinolones	10 (3.9)
Tetracyclines	12 (4.6)
Polymyxins	8 (3.1)
Aminoglycosides	26 (10)
TMP-SMX	13 (5)
Outcomes	
In-hospital mortality	69 (26.4)
90-day mortality	85 (38.3)
Functional status deterioration compared to preinfection status	80 (41.2)
Discharged to LTCF after being admitted from home	40 (18.0)
Additional hospitalizations within 6 months of isolation	126 (49.8)
Invasive procedures within 3 months of isolation	117 (45.3)
Bacteriological failure ^d	106 (40.6)
Median total LOS (days) (IQR)	14 (7–24.75)
Median LOS after isolation excluding those who died early (days) (IQR)	10 (7–16.5)

^a Data are from patients at the Detroit Medical Center between January 2005 and July 2010. IQR, interquartile range; TMP-SMX, trimethoprim-sulfamethoxazole; LTCF, long-term care facility; LTAC, long-term acute care facility; LOS, length of hospital stay; ICU, intensive-care unit; ESBL, extended-spectrum β -lactamase.

^b Values in parentheses are percentages unless otherwise noted. The percentages are calculated with the missing data excluded.

^c Including β -lactam/ β -lactamase inhibitor combinations.

^d Additional isolations of the same type of ESBL-producing bacteria in the 3 months following index isolation.

ertapenem (9). Sixty-nine patients died in the hospital (26.4%), and 85 patients died within 90 days (38.3%). In multivariate analysis, in-hospital mortality was significantly lower among patients who received carbapenems in their consolidative regimen ($n = 181$) than among those who received other *in vitro* active agents (14.9% versus 30%, respectively; adjusted OR = 0.39 [95% confidence interval {CI} = 0.16 to 0.95]; $P = 0.04$). The association

TABLE 2 Bivariate analyses comparing characteristics of patients with BSIs due to ESBL-producing *Enterobacteriaceae* who received ertapenem as consolidative therapy to those who received group 2 carbapenems^a

Parameter	Values (%) for patients receiving each therapy ^b		OR	95% CI	P value
	Ertapenem (n = 49)	Group 2 carbapenems ^c (n = 109)			
Demographic information					
Age (yr) (mean $\pm$ SD)	66.98 $\pm$ 18	65.52 $\pm$ 15.23			0.6
Elderly (≥ 65 years)	30 (61)	61 (56)	0.8	0.4–1.6	0.61
Type of infection					
<i>Escherichia coli</i>	36 (73.5)	49 (45)	3.3	1.5–7.6	0.001
Cocolonization with nonfermenters ^d	3 (6.1)	26 (23.9)	0.2	0.06–0.73	0.007
Source of bloodstream infection					
Urinary tract	30 (61.2)	41 (37.6)	2.62	1.31–5.24	0.01
Central line catheter	6 (12)	22 (20.2)	0.62	0.23–1.66	0.49
Status at admission					
Dependent functional status	35 (71)	71 (65.1)	1.34	0.64–2.79	0.47
Immunosuppressed state ^e	4 (8.2)	32 (29.4)	0.21	0.07–0.64	0.004
Charlson's weighted index comorbidity score (mean $\pm$ SD)	4.27 $\pm$ 2.75	4.3 $\pm$ 2.89			0.93
Exposure to health care setting					
Median LOS from admission to culture (days) (IQR)	0 (0–2.5)	2 (0–12)			0.002
Admitted from long-term care facility	30 (61)	64 (58.7)	1.11	0.56–2.21	0.86
ICU stay in current hospitalization	13 (27)	56 (51.4)	0.34	0.16–0.71	0.005
Severity of illness indices at time of ESBL isolation					
Rapidly fatal McCabe score ^f	8 (16)	21 (19.3)	0.82	0.33–2	0.83
Severe sepsis/septic shock/multiorgan failure	5 (10.2)	36 (33.3)	0.23	0.08–0.62	0.002

^a LOS, length of hospital stay. Consolidative therapy was given from day 3 to day 14 following the date of the culture at Detroit Medical Center between January 2005 and July 2010.^b Values are the numbers of patients (and percentages) unless otherwise noted. The percentages are calculated with the missing data excluded.^c Includes imipenem, meropenem, and doripenem.^d Defined as having *Acinetobacter baumannii* or *Pseudomonas aeruginosa* isolated in the period between 7 days before and 7 days after the isolation of the *Enterobacteriaceae*.^e Glucocorticoid therapy within the past month, anti-tumor necrosis factor α therapy in the past 6 months, chemotherapy or radiotherapy in the past 3 months, or HIV, a posttransplantation status, or neutropenia (white blood cell count < 500) at culture date.^f Expected to die within 2 months.

remained unchanged when patients who died early in the course of the disease were removed from analysis (in order to control for a potential selection bias).

An analysis was conducted comparing subjects who received ertapenem for empirical treatment ($n = 24$) to those who received empirical therapy with group 2 carbapenems ($n = 103$) after excluding patients who received both and those for whom the blood culture results were returned postmortem. Cases receiving ertapenem were significantly more likely to have a BSI secondary to *E. coli* ($P = 0.05$). Twenty-three patients (89%) receiving ertapenem had a low sepsis level, compared to 68 of subjects (66.7%) receiving a group 2 carbapenem ($P = 0.03$). The mean time to initiation of effective therapy was significantly longer in subjects receiving ertapenem than in patients receiving a group 2 carbapenem (59 h and 42.5 h, respectively; $P = 0.04$). In-hospital mortality occurred in 3 subjects (12%) treated empirically with ertapenem and 21 patients (20.4%) treated empirically with a group 2 carbapenem (OR = 0.51 [95% CI = 0.14 to 1.86]). Three-month mortality, deterioration in functional status, length of hospital stay, and other outcome measures demonstrated nonsignificant differences across the treatment groups. Sepsis level was the only variable which remained a significant predictor of in-hospital mortality ($P < 0.005$). Compared to group 2 carbapenem therapy, empirical

therapy with ertapenem was not associated with in-hospital mortality in a multivariate analysis (adjusted OR = 0.82 [95% CI = 0.17 to 3.81]; $P = 0.79$) controlling for the McCabe score, Charlson's weighted index comorbidity score, sepsis level, bacteremia source, time to effective therapy, or bacterium type. Similarly, 3-month mortality was not affected by carbapenem group (adjusted OR = 1.64 [95% CI = 0.23 to 11.49]; $P = 0.62$). Sepsis level, McCabe score at admission, Charlson's weighted index comorbidity score, bacteremia source, and receipt of empirical fluoroquinolones were significantly associated with 3-month mortality in a multivariate analysis.

Seventy-two patients received ertapenem for consolidative therapy, and 132 received group 2 carbapenems. After excluding patients who received both types of carbapenems, the comparative analysis included 49 patients who received ertapenem and 109 patients who received a group 2 carbapenem (Table 2). Subjects in the two groups had similar severities of illness (5). Patients receiving ertapenem were significantly more likely to have bacteremia from a urinary source ($P = 0.01$) and to have *E. coli* ESBL infection ($P = 0.001$). The length of hospital stay prior to ESBL-producing *Enterobacteriaceae* isolation was shorter in patients receiving ertapenem ($P = 0.002$), and patients receiving ertapenem were less likely to have been in the intensive care unit (ICU) prior to culture

TABLE 3 Bivariate analyses of outcomes of patients with BSIs due to ESBL-producing *Enterobacteriaceae* who were treated with ertapenem and those who were treated with group 2 carbapenems^a

Outcome parameter	No. of patients (% or IQR) with each outcome with indicated treatment		OR (95% CI)	P value
	Ertapenem (n = 49)	Group 2 carbapenem (n = 109)		
In-hospital mortality	3 (6.1)	20 (18.3)	0.29 (0.08–1.0)	0.05
90-day mortality	6 (15.8)	31 (33.3)	0.38 (0.14–0.99)	0.05
Functional status deterioration ^b	14 (30.0)	47 (52.2)	0.4 (0.19–0.85)	0.02
Discharged to LTCF ^c	3 (15.0)	12 (22.6)	0.61 (0.15–2.14)	0.75
Additional hospitalization ^d	33 (67.0)	56 (52.8)	1.84 (0.91–3.74)	0.12
Bacteriologic failures ^e	20 (41.0)	55 (50.5)	0.69 (0.34–1.42)	0.37
Median total LOS (days)	11 (8–17.5)	18 (9.5–32)		<0.01
Median LOS from culture to discharge (days) ^f	10 (7–14.5)	13 (8–21)		0.05

^a Data are from patients at the Detroit Medical Center between January 2005 and July 2010.^b Diminished ability to independently conduct ≥ 1 activities of daily living (18) compared to the status prior to infection.^c Discharge to a long-term care facility (LTCF) after being admitted from home.^d Additional hospitalization in the 6 months following discharge for those who survived the hospitalization.^e Additional isolations of the same organism in the 3 months following the date of the culture.^f Length of hospital stay (LOS) from culture to discharge after excluding the patients who died early.

($P = 0.005$). Severe levels of sepsis, per SIRS criteria, were significantly less common in the ertapenem-treated group than in the group 2 carbapenem-treated group (10% versus 33.3%, respectively; OR = 0.23; $P = 0.002$). In-hospital mortality occurred in three (6.1%) patients treated with ertapenem consolidative therapy and in 20 (18.3%) of the patients treated with group 2 carbapenems ($P = 0.05$) (Table 3). Mortality occurred within 90 days in six (15.8%) patients treated with ertapenem and in 31 (33.3%) patients treated with a group 2 carbapenem ($P = 0.05$). In a multivariate analysis, the type of carbapenem (group 1 versus group 2) was not associated with increased mortality (adjusted OR = 0.26; $P = 0.12$). Adjusted predictors of mortality included the severity of sepsis ($P < 0.005$) and the McCabe score at admission. After controlling for a propensity score of receiving ertapenem consolidative therapy, ertapenem was not associated with increased risk for death (OR = 0.50 [95% CI = 0.12 to 2.1]; $P = 0.34$). Similar results were noted for 90-day mortality in multivariate analyses utilizing a propensity score (OR = 0.51 [95% CI = 0.17 to 1.55]; $P = 0.23$) and those not using a propensity score (adjusted OR = 0.40; $P = 0.25$). Severe sepsis, the McCabe score at admission, and Charlson's index were significantly associated with 90-day mortality. In a subanalysis restricted to patients with severe sepsis ($n = 41$), three of five patients who received ertapenem as the main therapy died during the hospital stay (60%), compared to 13 of 36 patients who received group 2 carbapenems (36.1%) ($P = 0.36$).

There are no strict guidelines or policies pertaining to the preferred therapeutic management of infections due to ESBL-producing *Enterobacteriaceae*, although many consider carbapenems the preferred agents (1, 4, 8, 12, 14, 17, 19, 21, 24, 31). Among carbapenems, particularly for severe infections, many clinicians prefer to use a group 2 carbapenem rather than ertapenem (25). In this large cohort of patients with ESBL BSIs, carbapenems were associated with significantly better clinical outcomes than other antimicrobial classes, a result which is similar to findings of other investigators (8, 12, 17, 19, 21, 24, 31). Of particular interest, ertapenem was as effective as group 2 carbapenems in the treatment of ESBL BSIs. Although ertapenem was used for patients with less-invasive disease states and less-severe levels of sepsis, in multivariate and subgroup analyses controlling for differences in disease state and severity, ertapenem was as effective as group 2 car-

bapenems. It is notable that the study cohort consisted only of patients who had SIRS coupled with BSI. In terms of antimicrobial stewardship efforts geared toward limiting the emergence of carbapenem resistance among *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacteriaceae*, ertapenem should be considered an option for the treatment of ESBL BSIs. The findings in this study are consistent with previously published case series (3).

Although rare, reports of ESBL-producing *Enterobacteriaceae* with various levels of resistance to ertapenem have recently been published (16, 20). In the study cohort, according to 2009 CLSI breakpoints, two isolates (9.5%) were resistant to ertapenem (9).

The likelihood that a prospective, randomized, controlled trial that compares ertapenem and group 2 carbapenems for treatment of invasive infections due to ESBLs will be conducted in the near future is low. This large retrospective study provides the best available evidence to date regarding the efficacy of ertapenem in the treatment of ESBL BSIs. Based on these results, ertapenem should be considered a viable therapeutic option. Its relatively narrow spectrum of activity compared to that of other carbapenems is attractive from both antimicrobial stewardship and infection control perspectives.

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