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Research Article

Clinical Outcomes of Extended-Spectrum Beta-Lactamase-Producing *Enterobacteriaceae* Infections with Susceptibilities among Levofloxacin, Cefepime, and Carbapenems

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Purpose. Highly resistant Gram-negative bacterial infections are associated with high mortality. Increasing resistance to standard therapy illustrates the need for alternatives when treating resistant organisms, especially extended-spectrum beta-lactamase- (ESBL-) producing *Enterobacteriaceae*. *Methods*. A retrospective chart review at a community hospital was performed. Patients who developed ESBL-producing infections were included. Patients less than eighteen years old, who were pregnant, or who were incarcerated were excluded. The primary outcome was hospital mortality. The secondary outcomes included intensive care unit (ICU) mortality, ICU length of stay, and hospital length of stay. *Results*. 113 patients with ESBL-producing infections met the criteria for review. Hospital mortality: carbapenem (16.6%), cefepime (0%), and levofloxacin (15.3%) ($p = 0.253$). ICU mortality: carbapenem (4.5%), cefepime, (0%), and levofloxacin (3.7%) ($p = 0.616$). Mean ICU and hospital length of stay: carbapenem (9.8 ± 16, 12.1 ± 1 days), cefepime (7.8 ± 6, 11.1 ± 10.5 days), and levofloxacin (5.4 ± 4.1, 11.1 ± 10.4 days) ($p = 0.805, 0.685$). No predictors were clearly found between the source of infection and mortality. *Conclusion*. Cefepime or levofloxacin can be a potential alternative agent for infections with ESBL-producing *Enterobacteriaceae*, and larger clinical trials investigating these outcomes are warranted.

1. Introduction

Extended-spectrum beta-lactamase- (ESBL-) producing *Enterobacteriaceae* infections are increasingly identified with subsequent hospitalization [1, 2]. ESBL is a resistance mechanism in which the beta-lactam ring of antibiotics such as penicillins, cephalosporins, and aztreonam is hydrolyzed, inactivating the antibiotic. Increasing resistance was demonstrated in a 2013 Centers for Disease Control and Prevention (CDC) report, which included 26,000 ESBL-producing *Enterobacteriaceae* infections and 1700 deaths in the United States [3]. Traditionally, the treatment of choice for ESBL-producing *Enterobacteriaceae* infections has been the carbapenem class. However, trends in resistance demonstrate the need of conservative use of carbapenems and illustrate the need for alternative therapies against ESBL-producing organisms. Additionally, chromosomally mediated inducible resistance has manifested as porin loss, which decreases drug entry in strains already retaining high levels of AmpC [4]. Emerging incidence of community-acquired ESBL-identified infections has demonstrated a positive association with the increasing trend of carbapenem resistance in *Enterobacteriaceae*. Though prospective research demonstrating effectiveness of other therapies has been limited, there is emerging retrospective evidence in support of the use of cefepime, fluoroquinolones, and piperacillin/tazobactam in certain clinical situations [5–10].

It is of interest to the patient for organisms (*E. coli* being the most common to exhibit ESBLs) to be detected and reported to healthcare providers in a timely fashion for both appropriate treatment to be initiated and resulting morbidity and mortality to be significantly reduced. However, reporting

of ESBL can be delayed by a few days due to the screening and identification process. Many microbiology laboratories are challenged by increasingly changing and complicated recommendations [11]. Minimum inhibitory concentrations (MICs) of β-lactamase-producing *Enterobacteriaceae* might be reported as high but are still in the susceptible range (i.e., "hidden resistance") [7, 8]. If diagnostic microbiology laboratories are unable to adequately test for ESBL production, it could be argued that suspect cases of hidden resistance will go unrecognized by the microbiologists and clinicians, increasing the likelihood for adverse consequences [8–10]. Other data showed that carbapenem use when MIC is ≥4 mg/liter had outcomes of increased mortality compared to patients whose microbiological isolate MICs were lower, demonstrating carbapenem therapy limitations [12].

Because *Enterobacteriaceae* organisms are becoming increasingly resistant to standard therapy, treatment selected by interpretation of MICs of ESBL producers and by clinical outcome may offer therapeutic alternatives in more challenging situations [7, 12–14]. Appealing to the cause of antimicrobial stewardship, the fourth-generation cephalosporin cefepime could be a considerable alternative against ESBL-producing organisms and could shift trends for carbapenem use. Cefepime has shown to have greater, stable activity against ESBL (i.e., AmpC enzymes) compared to the other extended-spectrum cephalosporins [9, 10, 14]. Cefepime does not rely on porins for entry into the bacterial cell, making it useful in the down-regulated porin resistance mechanism [15, 16]. Appealingly, cefepime could be used in therapy for ESBL-EC and ESBL-K strains highly resistant to third-generation cephalosporins (including ceftazidime) and to aztreonam [14, 17–21]. Fluoroquinolones may also offer a place as alternative therapy in treating ESBL-producing *Enterobacteriaceae*. Though many bacteria are becoming increasingly resistant to fluoroquinolones, treatments with this class when susceptibilities allow have demonstrated improved inpatient mortality when compared to carbapenems [22–25]. A small retrospective review with in vitro samples indicated no difference in inpatient mortality with levofloxacin when comparing low, intermediate, and high MICs. However, they did demonstrate trends for a shorter improved mortality and shorter length of stay in the lower MIC group [22].

The objective of this study is to evaluate clinical outcomes among levofloxacin, cefepime, and carbapenem used for ESBL-producing *Enterobacteriaceae* infections. Additional objectives include identifying risk factors that can help tailor antibiotic therapy.

2. Methods

This is a retrospective chart review conducted at one 522 (including 22 ICU) bed tertiary community medical center. Patient charts were included from January 1, 2012, to September 30, 2015. Records and profiles of discharged patients who received cefepime, levofloxacin, or carbapenem for ESBL pathogens within the specified time span were identified by the microbiology lab department. This study received approval by the Texas Tech University Health Sciences Center Institutional Review Board. Individuals with ESBL-producing *Enterobacteriaceae* infections were identified, who also waived the need for informed consent. Eligible patients fulfilled each of the following criteria: (1) aged 18 years or older, (2) clinically diagnosed with the ESBL-producing *Enterobacteriaceae* isolate demonstrated on culture, (3) received empirical treatment with cefepime, levofloxacin, or carbapenem for at least 48 hours after initial cultures had been drawn, and (4) admitted for inpatient treatment. Ninety days prior to culture, risk factors were identified. The researchers took no part in the conduct of the study, nor did they play a role in the analysis of the data.

An infection occurring in the ICU was defined as the patient being present in the ICU when the culture was identified for the Gram-negative organism. Infectious and other diagnoses were identified by ICD-9 codes in the patient chart. Acute renal failure is identified when the serum creatinine is increased by 50% or more from the patient's baseline serum creatinine on the onset of infection. Included in this were patients with a past medical history of chronic kidney disease (CKD) noted in the chart. Antimicrobial therapy administered after diagnosis was regarded as empirical treatment, and therapy administered afterward was defined as definitive therapy.

This single medical center has a centralized clinical microbiology laboratory which processes 96,000 samples annually. At this laboratory, bacteria can be identified down to a genus species, and the susceptibilities are further outlined by predefined antimicrobials. An automated broth microdilution system (MicroScan; Siemens AG, Germany) allows for susceptibility reporting, and an analysis is conducted in accordance with the Clinical and Laboratory Standards Institute (CLSI) criteria [26]. To identify ESBL-producing bacteria, isolates are processed using the MicroScan WalkAway system. This system initially screens for ceftazidime and cefpodoxime resistance, which is subsequently confirmed on demonstration of synergy between these two antibiotics and additionally by clavulanic acid on disc synergy testing. The interpretation followed the current breakpoints recommended by the CLSI. The severity of underlying medical illness was calculated by the Elixhauser scoring system [27].

The primary study outcome was hospital mortality. The secondary outcomes were ICU mortality, ICU length of stay, and hospital length of stay.

The following baseline characteristics were also collected: age, gender, type of infection, source of infection, culture species, and sensitivities.

All analyses were performed using Strata Version 13.1 (StataCorp, College Station, TX). Descriptive statistics were used to quantify patient characteristics, as well as for analysis of the primary and secondary outcomes. Categorical variables were expressed as percentages of total numbers of patients analyzed. Continuous variables were expressed as mean values ± SDs. The Kruskal–Wallis test was used to compare differences between groups. Multivariate regression analyses were used to identify risk factors that may have association with clinical outcomes. Data are summarized as n (%). Adjusted odds ratios (ORs) are presented with 95% confidence intervals and were calculated using

Table 1: Baseline characteristics.

Characteristics	Carbapenem ($n = 66$)	Cefepime ($n = 21$)	Levofloxacin ($n = 26$)	p value
Demographics				
Age (years), mean (SD)	69.5 (15.9)	67.5(10.5)	72.5 (12.8)	0.357
Gender				0.065
Female, *n* (%)	41 (62.1)	8 (38.1)	19 (70.4)	
Male, *n* (%)	25 (37.9)	13 (61.9)	8 (29.6)	
Comorbidity score, mean (SD)	14.7 (10.4)	10 (8.4)	14.4 (13.1)	0.213
Type of infection				
Hospital acquired, *n* (%)	21 (31.8)	1 (4.8)	8 (29.6)	0.046
Healthcare associated*, *n* (%)	21 (31.8)	6 (28.6)	10 (37)	0.814
Community acquired, *n* (%)	24 (36.4)	13 (61.9)	9 (33.3)	0.082
Source of infection				
Catheter LSI, *n* (%)	0 (0)	1 (4.8)	0 (0)	0.109
Bacteremia, *n* (%)	4 (6.1)	2 (9.5)	3 (11.1)	0.684
Septic shock, *n* (%)	8 (12.1)	2 (9.5)	5 (18.5)	0.614
Intra-abdominal, *n* (%)	5 (7.6)	0 (0)	2 (7.4)	0.434
Pneumonia, *n* (%)	7 (10.6)	1 (4.8)	1 (3.7)	0.452
SSTI, *n* (%)	10 (15.2)	6 (28.6)	2 (7.4)	0.136
UTI, *n* (%)	44 (66.7)	12 (57.1)	19 (70.4)	0.618
Culture species				
E. coli, *n* (%)	51 (77.3)	18 (85.7)	24 (88.9)	0.369
K. pneumoniae, *n* (%)	11 (16.7)	1 (4.8)	1 (3.7)	0.118
P. mirabilis, *n* (%)	15 (22.7)	5 (23.8)	0 (0)	0.024

*Healthcare-associated infections = acquired in nursing resident or recent hospitalization.

multivariate logistic regression. OR p values correspond to adjusted ORs.

3. Results

3.1. Baseline Characteristics. In this review, 113 patients with ESBL-producing *Enterobacteriaceae* infections were successfully identified at the community hospital during the 3-year study period (Table 1). 66 patients were in the carbapenem group, 21 in the cefepime group, and 26 in the levofloxacin group. Table 1 shows the characteristics of the patients at baseline. The mean age of the patients was 69.8 years, and 60% were female. There were 77.3% patients in the carbapenem group, 85.7% in the cefepime group, and 88.9% in the levofloxacin where the pathogen was identified as *E. coli*. The predominant infection treated was urinary tract infection (UTI) with 66.7% in the carbapenem group, 57.1% in the cefepime group, and 70.4% in the levofloxacin group. Additionally, 7.6% in the carbapenem group, 0% in the cefepime group, and 7.4% in the levofloxacin group were treated for intra-abdominal infection. Therefore, no patients were treated with cefepime for intra-abdominal infection.

Furthermore, 15.2% in the carbapenem group, 28.6% in the cefepime group, and 7.4% in the levofloxacin group were treated for skin and soft tissue infection (SSTI). Of note, carbapenem and levofloxacin groups were treated for over 60% hospital-acquired or healthcare-associated infections, while the cefepime group was treated for 61.9% community-acquired infections.

3.2. Primary and Secondary Outcomes. Hospital mortality and ICU mortality were not different in all three groups. No one died in the cefepime group even though there was no statistical difference (Table 2). ICU length of stay was shorter in the cefepime and levofloxacin groups, by 2.0 and 4.4 days, respectively. Hospital length of stay was shorter by 1 day in the cefepime and levofloxacin groups compared to the carbapenem group, although this was not statistically different.

3.3. Multivariate Analysis. There were no predictors found between the source of infection and mortality (Table 3).

4. Discussion

There is controversy in recent literature regarding alternative therapies against infections due to ESBL-producing *Enterobacteriaceae*. This study has outlined outcomes for a rural healthcare system where cefepime and levofloxacin were used as alternatives for treatment of infections.

Studies demonstrate improved inpatient mortality when susceptibilities have allowed treatment with fluoroquinolones such as ciprofloxacin and levofloxacin [22–24]. However, most of these studies only studied bacteremia as the primary type of infection, whereas our study allowed for all types of infection. Furthermore, these studies were following the earlier break points of MIC susceptibility established by the CLSI. Antimicrobial sensitivity to cefepime and levofloxacin among *Enterobacteriaceae* is defined by the 2014 CLSI update as an

Table 2: Primary and secondary outcomes.

Outcome	Carbapenem ($n = 66$)	Cefepime ($n = 21$)	Levofloxacin ($n = 26$)	p value
Primary				
Expired patients in hospital, n (%)	11 (16.6)	0 (0)	4 (15.4)	0.253
Secondary				
Expired patients in ICU, n (%)	3 (4.5)	0 (0)	1 (3.7)	0.616
ICU length of stay, mean (SD)	9.8 (16.0)	7.8 (6)	5.4 (4.1)	0.805
Hospital length of stay, mean (SD)	12.1 (11)	11.1 (10.5)	11.1 (10.4)	0.685

Table 3: Multivariate analysis.

	Mortality		Unadjusted OR	Adjusted OR	p
	No ($n = 99$)	Yes ($n = 15$)			
Vascular catheter LSI	1 (1.0)	0 (0.0)	—	—	—
CLSI	0 (0.0)	0 (0.0)	—	—	—
Ventilator-related infection	0 (0.0)	0 (0.0)	—	—	—
Bacteremia	8 (8.1)	1 (6.7)	0.81 (0.02–6.92)	0.63 (0.07–6.08)	0.692
Sepsis shock	14 (14.1)	1 (6.7)	0.43 (0.01–3.34)	0.31 (0.03–3.00)	0.314
Intra-abdominal infection	7 (7.1)	0 (0.0)	0.00 (0.00–3.57)	—	—
Pneumonia	6 (6.1)	3 (20.0)	3.87 (0.54–20.9)	2.28 (0.26–20.15)	0.458
Skin and soft tissue infection	17 (17.2)	1 (6.7)	0.34 (0.01–2.59)	0.26 (0.02–2.97)	0.278
Urinary tract infection	66 (66.7)	9 (60.0)	0.75 (0.21–2.79)	0.53 (0.10–2.84)	0.461

MIC of less than or equal to 2 μg/mL [26]. A randomized control trial by Seo et al. demonstrated a high treatment failure comparing cefepime, piperacillin/tazobactam, and ertapenem in treatment of ESBL-producing *E. coli* infection [28]. However, the baseline characteristics of patients in the study were not well aligned. The sex differences between cefepime and the other 2 groups varied, as well as the average age of patients in the cefepime group was approximately 10 years greater than the piperacillin/tazobactam and ertapenem groups. Our study, however, showed similar reporting between ages and sexes.

Previous literature showed an association between clinical outcomes and MICs. These studies have suggested that a low MIC value is positively associated with better clinical outcomes versus a higher MIC [9, 10, 17, 19–22]. Recent literature has trended favorably from a sensitivity-based approach to an MIC-based approach in settings where ESBL producers are endemic [29–31]. Studies have shown that cefepime and levofloxacin can both favorably achieve pharmacodynamic targets against isolates of fully susceptible *Enterobacteriaceae* at lowered MIC susceptibilities [11, 12, 15, 18, 22]. There have been underlying issues with studies regarding the lack of clinical experience using these medications, as well as the conflicting reports of clinical outcomes in the literature when studying treatments for ESBL-producing *E. coli* infection. Additional research would help demonstrate that drug target attainment in ESBL-producing *Enterobacteriaceae* with cefepime and levofloxacin will achieve adequate drug target levels when using the recent updates for susceptible breakpoints for cefepime and levofloxacin.

Additionally, the doses of cefepime used in the study may have been subtherapeutic, whereas our doses were reviewed for therapeutic efficacy and we also took into account if renal dose adjustments had been made [28]. Lower doses of cefepime have been associated with treatment failure and higher mortality [28, 32]. Literature suggests that higher maximal doses of cefepime, even when renally adjusted, may be more beneficial than standard cefepime dosing [32]. Because time above MIC is critical for clinical success of cefepime dosing, our study evaluated if the dose was appropriate based on the infection type and renal function [32, 33].

Previous retrospective chart review had observed a trend of lower 30-day mortality in the fluoroquinolone group compared to the carbapenem group, although not statistically significant (OR 4.53; 95% CI 0.98–21) [23]. Similarly, a higher 30-day mortality in the cefepime group was demonstrated when CLSI breakpoints were 8 or greater (OR 7.1; 95% CI 2.5–20.3) [21]. However, unlike our study, these two trials only looked at bacteremia infection and had used previously defined CLSI breakpoints for cefepime. Although this study did not find a statistically significant difference either, when using a lower MIC breakpoint, there was a trend for lower mortality for both alternative therapy groups. Thereby, it was suggested that cefepime therapy was limited for bacteremia caused by ESBL-producing *Enterobacteriaceae* organisms when cefepime MIC was less than or equal to 1 μg/mL [21, 23]. Additional comparisons of length of hospital stay had shown that higher MIC resulted in increased length of stay of 5.67 days (95% CI 0.77–10.62 days; $p = 0.02$) with levofloxacin [22]. Similar to other studies, our study was limited by allowing other antimicrobial agents that could have altered the outcomes, although matched group analysis was applied to our study to offset this limitation.

Our study did not identify a statistically significant difference in hospital mortality between patients who were receiving treatment with carbapenem and those who received an alternative treatment. However, this study did find a trend between carbapenem therapy and an increased risk of mortality and alternative therapy and a decreased risk of mortality. It follows that there might be greater in vitro activity in favor for cefepime, specifically for not being induced by the AmpC gene. Interestingly, no one died in the cefepime group even though there was no statistical difference. This could be explained by many community-acquired infections in the cefepime group, but this suggests that cefepime can be a good treatment option in ESBL community-acquired infections. Carbapenem therapy was associated with a trend for longer hospital stay than with cefepime therapy. This association is not entirely clear but is possibly related to increased level of severity of illness among patients receiving carbapenem therapy. More patients with septic shock and pneumonia were included in the carbapenem group, and more community-acquired infections were in the cefepime group. Although unable to demonstrate an association between mortality and source of infection for patients receiving cefepime or levofloxacin, it is possible that this study was underpowered to identify an association. Although unable to demonstrate an association between increased MIC of cefepime and mortality among patients receiving cefepime monotherapy, it is possible that the results might have been diluted due to the inability to detect definitive MIC values.

Our study had a few strengths. First, this research was specifically looking at clinical outcomes for the hospital and ICU. Additionally, this study allowed for identification of multiple *Enterobacteriaceae* organisms. This study also allowed for several types of infection. Up until this point, previous literature had been limited to specific types of *Enterobacteriaceae* (e.g., only *E. coli*) and had only studied outcomes in cases of bacteremia or UTI.

This study did have several limitations. First, there was a low sample size for the cefepime and levofloxacin groups compared to the carbapenem group. This is likely due to the physician's preference for the carbapenem group. Carbapenem therapy is used in this healthcare setting predominantly for ESBL-producing *Enterobacteriaceae*. Additionally, it was challenging to determine the exact MIC, as the MIC reported used automated $\log_2$ dilution. In previous literature, an MIC of 1 or less proved to have a positive association between cefepime therapy and mortality. If this study had been able to detect an exact MIC of 1, there might have been a better detection for outcomes. Finally, there potentially was a physician selection bias for cefepime therapy in patients receiving treatment for community-acquired ESBL-producing infections.

5. Conclusion

Results from this study suggest that either cefepime or levofloxacin can be a potential alternative agent for infections with ESBL-producing *Enterobacteriaceae* for hospitalized patients when isolates are susceptible. Further studies with larger sample size and well-balanced type of infections between groups are warranted.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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References

[1] J. D. Pitout, "Infections with extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: changing epidemiology and drug treatment choices," *Drugs*, vol. 70, no. 3, pp. 313–333, 2010.

[2] R. Ben-ami, M. J. Schwaber, S. Navon-venezia et al., "Influx of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* into the hospital," *Clininical Infectious Diseases*, vol. 42, no. 7, pp. 925–934, 2006.

[3] Antibiotic resistance threats in the United States," 2017, http://www.cdc.gov/drugresistance/threat-report-2013.

[4] M. E. Falagas and D. E. Karageorgopoulos, "Extended-spectrum beta-lactamase-producing organisms," *Journal of Hospital Infection*, vol. 73, no. 4, p. 354, 2009.

[5] K. A. Wani, M. A. Thakur, A. Siraj fayaz, B. Fomdia, B. Gulnaz, and P. Maroof, "Extended spectrum B-lactamase mediated resistance in *Escherichia coli* in a tertiary care hospital," *International Journal of Health Sciences*, vol. 3, no. 2, pp. 155–163, 2009.

[6] M. Muhammed, M. E. Flokas, M. Detsis, M. Alevizakos, and E. Mylonakis, "Comparison between carbapenems and β-lactam/β-lactamase inhibitors in the treatment for bloodstream infections caused by extended-spectrum β-lactamase-producing *Enterobacteriaceae*: a systematic review and meta-analysis," *Open Forum Infectious Diseases*, vol. 4, no. 2, p. ofx099, 2017.

[7] S. V. Bhat, A. Y. Peleg, T. P. Lodise et al., "Failure of current cefepime breakpoints to predict clinical outcomes of bacteremia caused by gram-negative organisms," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 12, pp. 4390–4395, 2007.

[8] M. Ghatole, P. Manthalkar, S. Kandle, V. Yemul, and V. Jahagirdar, "Correlation of extended spectrum beta lactamases production with cephalosporin resistance in gram negative bacilli," *Indian Journal of Pathology and Microbiology*, vol. 47, no. 1, pp. 82–84, 2004.

[9] G. Kahlmeter, "Breakpoints for intravenously used cephalosporins in *Enterobacteriaceae*–EUCAST and CLSI breakpoints," *Clinical Microbiology and Infection*, vol. 14, pp. 169–174, 2008.

[10] D. L. Paterson, W. C. Ko, A. Von gottberg et al., "Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum beta-lactamases: implications for the clinical microbiology laboratory," *Journal of Clinical Microbiology*, vol. 39, no. 6, pp. 2206–2212, 2001.

[11] D. L. Paterson, L. Mulazimoglu, J. M. Casellas et al., "Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in *Klebsiella pneumoniae* isolates causing bacteremia," *Clinical Infectious Diseases*, vol. 30, no. 3, pp. 473–478, 2000.

[12] J. S. Esterly, J. Wagner, M. M. Mclaughlin, M. J. Postelnick, C. Qi, and M. H. Scheetz, "Evaluation of clinical outcomes in patients with bloodstream infections due to Gram-negative bacteria according to carbapenem MIC stratification," *Antimicrobial Agents and Chemotherapy*, vol. 56, no. 9, pp. 4885–4890, 2012.

[13] A. Wong-beringer, J. Hindler, M. Loeloff et al., "Molecular correlation for the treatment outcomes in bloodstream infections caused by *Escherichia coli* and *Klebsiella pneumoniae* with reduced susceptibility to ceftazidime," *Clinical Infectious Diseases*, vol. 34, no. 2, pp. 135–146, 2002.

[14] P. C. Kohner, F. J. Robberts, F. R. Cockerill, and R. Patel, "Cephalosporin MIC distribution of extended-spectrum-β-lactamase- and pAmpC-producing *Escherichia coli* and *Klebsiella* species," *Journal of Clinical Microbiology*, vol. 47, no. 8, pp. 2419–2425, 2009.

[15] R. G. D'angelo, J. K. Johnson, J. T. Bork, and E. L. Heil, "Treatment options for extended-spectrum beta-lactamase (ESBL) and AmpC-producing bacteria," *Expert Opinion Pharmacotherapy*, vol. 17, no. 7, pp. 953–967, 2016.

[16] P. G. Ambrose, S. M. Bhavnani, and R. N. Jones, "Pharmacokinetics-pharmacodynamics of cefepime and piperacillin-tazobactam against *Escherichia coli* and *Klebsiella pneumoniae* strains producing extended-spectrum beta-lactamases: report from the ARREST program," *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 5, pp. 1643–1646, 2003.

[17] G. Zanetti, F. Bally, G. Greub et al., "Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study," *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 11, pp. 3442–3447, 2003.

[18] S. Y. Lee, J. L. Kuti, and D. P. Nicolau, "Cefepime pharmacodynamics in patients with extended spectrum beta-lactamase (ESBL) and non-ESBL infections," *Journal of Infection*, vol. 54, no. 5, pp. 463–468, 2005.

[19] T. Chopra, D. Marchaim, J. Veltman et al., "Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*," *Antimicrobial Agents and Chemotherapy*, vol. 56, no. 7, pp. 3936–3943, 2012.

[20] H. M. Nguyen, K. L. Shier, and C. J. Graber, "Determining a clinical framework for use of cefepime and β-lactam/β-lactamase inhibitors in the treatment of infections caused by extended-spectrum-β-lactamase-producing *Enterobacteriaceae*," *Journal of Antimicrobial Chemotherapy*, vol. 69, no. 4, pp. 871–880, 2014.

[21] N. Y. Lee, C. C. Lee, W. H. Huang, K. C. Tsui, P. R. Hsueh, and W. C. Ko, "Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: MIC matters," *Clinical Infectious Diseases*, vol. 56, no. 4, pp. 488–495, 2013.

[22] R. Defife, M. H. Scheetz, J. M. Feinglass, M. J. Postelnick, and K. K. Scarsi, "Effect of differences in MIC values on clinical outcomes in patients with bloodstream infections caused by gram-negative organisms treated with levofloxacin," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 3, pp. 1074–1079, 2009.

[23] C. Lo, C. Lee, C. C. Li et al., "Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*," *Journal of Microbiology, Immunology and Infection*, vol. 50, no. 3, pp. 355–361, 2015.

[24] L. Drago, E. De vecchi, B. Mombelli, L. Nicola, M. Valli, and M. R. Gismondo, "Activity of levofloxacin and ciprofloxacin against urinary pathogens," *Journal of Antimicrobial Chemotherapy*, vol. 48, no. 1, pp. 37–45, 2001.

[25] M. P. Fink, D. R. Snydman, M. S. Niederman et al., "Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin: The Severe Pneumonia Study Group," *Antimicrobial Agents and Chemotherapy*, vol. 38, no. 3, p. 547, 1994.

[26] Clinical Laboratory Standards Institute, "Performance standards for antimicrobial susceptibility testing," Twenty-fourth informational supplement ed. CLSI document M100–S24, 2017, https://www.researchgate.net/file.PostFileLoader.html?id=59202a0696b7e4d462166956&assetKey=AS%3A496054988533760%401495280134033.

[27] A. Garland, R. Fransoo, K. Olafson et al., *The Epidemiology and Outcomes of Critical Illness in Manitoba*, Manitoba Centre for Health Policy, Winnipeg, MB, Canada, 2012, http://mchp-appserv.cpe.umanitoba.ca/reference/MCHP_ICU_Report_WEB_(20120403).pdf.

[28] Y. B. Seo, J. Lee, Y. K. Kim et al., "Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli*," *BMC Infectious Diseases*, vol. 17, no. 1, p. 404, 2017.

[29] R. Ramphal and P. G. Ambrose, "Extended-spectrum beta-lactamases and clinical outcomes: current data," *Clinical Infectious Diseases*, vol. 42, no. 4, pp. s164–s172, 2006.

[30] C. I. Kang, S. H. Kim, W. B. Park et al., "Bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 12, pp. 4574–4581, 2004.

[31] D. L. Paterson, "Resistance in gram-negative bacteria: *Enterobacteriaceae*," *American Journal of Medicine*, vol. 119, no. 6, pp. S20–S28, 2006.

[32] N. Andreatos, M. E. Flokas, A. Apostolopoulou, M. Alevizakos, and E. Mylonakis, "The dose-dependent efficacy of cefepime in the empiric management of febrile neutropenia: a systematic review and meta-analysis," *Open Forum Infectious Diseases*, vol. 4, no. 3, p. ofx113, 2017.

[33] C. Miglis, N. J. Rhodes, J. L. Kuti, D. P. Nicolau, S. A. Van wart, and M. H. Scheetz, "Defining the impact of severity of illness on time above the MIC threshold for cefepime in Gram-negative bacteraemia: a 'Goldilocks' window," *International Journal of Antimicrobial Agents*, vol. 50, no. 3, pp. 487–490, 2017.