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The Use of Noncarbapenem β-Lactams for the Treatment of Extended-Spectrum β-Lactamase Infections

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The continued rise in infections caused by extended-spectrum β-lactamase (ESBL)–producing pathogens is recognized globally as one of the most pressing concerns facing the healthcare community. Carbapenems are widely regarded as the antibiotics of choice for the treatment of ESBL-producing infections, even when in vitro activity to other β-lactams has been demonstrated. However, indiscriminant carbapenem use is not without consequence, and carbapenem overuse has contributed to the emergence of carbapenem-resistant Enterobacteriaceae. The use of non-carbapenem β-lactams for the treatment of ESBL infections has yielded conflicting results. In this review, we discuss the available data for the use of cephamycins, cefepime, piperacillin-tazobactam, ceftolozane-tazobactam, and ceftazidime-avibactam for the treatment of ESBL infections.

Keywords. ESBLs; carbapenems; cephamycins; cefepime; piperacillin-tazobactam.

Since their description in the 1980s, extended-spectrum β-lactamase (ESBL)–producing organisms have been recognized as a global threat [1–4]. Through the years, these enzymes have undergone substantial biochemical alterations resulting in the ability to more efficiently hydrolyze β-lactam antibiotics [5].

ESBLs have been detected worldwide in several gram-negative genus and species; however, they are most prevalent among *Escherichia coli* and *Klebsiella* species.

Carbapenems are widely regarded as the antibiotics of choice for the treatment of ESBL-producing infections, even when in vitro activity to other β-lactams is demonstrated [6, 7]. They are stable to ESBL hydrolytic activity and numerous studies demonstrate their efficacy [6]. However, carbapenem overutilization stimulates various resistance pathways including outer membrane protein (OMP) mutations and the selection of β-lactamases capable of hydrolyzing carbapenems [8]. Whenever equally efficacious alternate agents exist, efforts should be made to limit the use of carbapenem antibiotics.

The increased hydrolytic activity of ESBLs against third-generation cephalosporins, particularly ceftriaxone and cefotaxime, and their associated poor outcomes, usually disqualifies them from consideration for the treatment of ESBL-associated infections [9]. However, there are a number of scenarios that give us pause as to whether other noncarbapenem β-lactams can be prescribed in place of carbapenems (Table 1).

In this review, we will summarize the data available on the use of noncarbapenem β-lactams compared to carbapenems for the treatment of ESBL infections. Our review is limited to antibiotics available in the United States, with the most in-depth discussion focused on piperacillin-tazobactam, as this agent appears to arouse the greatest debate. To date, there have been no adequately powered randomized controlled trials evaluating the use of β-lactam agents for ESBL infections. Therefore, we are left with weighing the pros and cons of available observational studies (Table 2), while accounting for the inherent limitations of this study design. Although we will not formally discuss non–β-lactam options in this review, several non–β-lactam options deserve consideration for the treatment of ESBL infections when susceptible in vitro, with some stipulations based on the source of infection and severity of illness.

CEPHAMYCINS

Cephamycins demonstrate consistent in vitro activity against ESBL-producing Enterobacteriaceae isolates, distinguishing them from AmpC cephalosporinases [10]. Concerns with administering cephamycins for the treatment of ESBL infections stem from reports demonstrating acquisition of OMP mutations and/or plasmids encoding AmpC cephalosporinases during exposure to these agents [11–14]. In at least 1 published case, a patient with a *K. pneumoniae* ESBL isolate became resistant to both flomoxef and carbapenem therapy, after exposure to flomoxef, due to an OMPk36 mutation, in combination with acquisition of the plasmid-mediated AmpC cephalosporinase gene bla_{DHA-1} [14]. It is unclear how frequently such mutations

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Table 1. Potentially Favorable Circumstances for Noncarbapenem-β-Lactams in the Treatment of Extended-Spectrum β-Lactamase Infections

• What if noncarbapenem β-lactam minimum inhibitory concentrations are low?
• What if high-dose, frequent-interval βL-βLIs or cefepime is administered?
• What if extended-infusion noncarbapenem β-lactams are administered?
• If carbapenem antibiotics are administered when the burden of bacteria is highest, can therapy be transitioned to a noncarbapenem after a short period of time?
• If a βL-βLI is administered, does the type of β-lactamase inhibitor matter (eg, tazobactam, sulbactam, clavulanic acid, or avibactam)?
• Does it matter if the ESBL resistance mechanism is a bla_{TEM} type, bla_{CTX-M} type, or bla_{SHV} type?
• Does the genus or species of the ESBL producer matter?
• Does the source of bacteremia and if source control measures were taken matter?
• Should the severity of illness determine if a carbapenem or noncarbapenem agent is administered?

Abbreviations: βL-βLI, β-lactam–β-lactamase inhibitor; ESBL, extended-spectrum β-lactamase.

and gene acquisitions occur and what the predisposing host and environmental factors are.

A number of cephamycins are commercially available including cefoxitin, cefotetan, cefmetazole, flomoxef, and moxalactam. Unfortunately, clinical data evaluating cephamycins for ESBL infections are scarce, and data comparing the relative efficacy of the various cephamycins are virtually nonexistent. Existing observational studies comparing cephamycins and carbapenems are plagued by the inherent limitations of observational studies—most notably confounding by indication—as well as small sample sizes (Table 2) [15–20]. Only 1 of these studies showed improved outcomes among ESBL-infected patients treated with carbapenems compared with cephamycins, while the others could not detect differences [18] (Table 3). Optimal dosing regimens and achievable target attainment for various cephamycin minimum inhibitory concentrations (MICs) need to be explored [21].

Table 2. Select Limitations of Existing Observational Studies Comparing Noncarbapenem β-Lactam Antibiotics and Carbapenems for the Treatment of Extended-Spectrum β-Lactamase Infections

• Inconsistent criteria for extended-spectrum β-lactamase production
• Confounding by indication (ie, ill-appearing patients more likely to receive the more "aggressive" therapy, ie, carbapenems)
• Differences in outcomes definitions
• Delays in initiating appropriate antibiotic therapy
• Classification issues for patients initially receiving empiric noncarbapenem β-lactam therapy, then transitioned to carbapenem therapy
• Large proportions of patients receiving combination antibiotic therapy
• Often single-center experiences
• Sample sizes limit sufficient power to detect differences between treatment approaches, if such differences exist
• Insufficient subgroups for analysis (eg, proportion of *Escherichia coli* vs *Klebsiella pneumoniae*, proportion of bla_{CTX-M} vs bla_{SHV})
• Disproportionate numbers of patients with low-inoculum and high-inoculum infections
• Differences in antibiotic susceptibility criteria utilized
• Differences in local epidemiology of in vitro activity of noncarbapenem β-lactams
• Insufficient data on dosing regimens
• Insufficient data on clinical outcomes with extended-infusion β-lactam therapy

We believe that cephamycins may be useful agents in the treatment of nonsevere ESBL-producing infections from urinary sources. Given the limited data on nonurinary sources and severe infections, it is the opinion of the authors that the use of cephamycins for severe ESBL infections and those originating outside of the urinary tract should be avoided until more data are available.

CEFEPIME

Cefepime is an oxyimino-cephalosporin agent with enhanced stability against degradation by β-lactamases. The current European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints for cefepime are 1 μg/mL and 8 μg/mL (accounting for drug dosing), respectively [22, 23]. There is concern that the current CLSI cefepime breakpoint leaves some ESBL enzymes in the susceptible range (ie, "hidden resistance)" [24].

Concerns about the diminished efficacy of cefepime for the treatment of ESBL infections with higher bacterial inoculums (eg, intra-abdominal infections, pneumonia, osteoarticular infections) have tempered enthusiasm for the use of cefepime for this indication. This so called "inoculum effect," in which drug MICs increase dramatically in the presence of an increased bacterial load despite apparent initial susceptibility, has been observed in both in vitro and animal studies [25–31]. Highlighting one experience, Burgess and colleagues evaluated cefepime and meropenem against standard- and high-inoculum ESBL *Klebsiella pneumoniae* infections [32]. Each of these antibiotics maintained bactericidal activity against standard inoculums but at high inoculums, in contrast to meropenem, cefepime was unable to sustain bactericidal activity against ESBL producers. In this same series of experiments, both agents maintained >99% killing of high-inoculum non-ESBL infections over a 24-hour observation period. The contribution of the inoculum effect toward treatment failures has not been the subject of comprehensive clinical review.

Apart from the inoculum effect, an alternative explanation for poor outcomes associated with cefepime therapy relates to failure to meet necessary pharmacodynamic targets due to inadequate dosing and/or interval schedules [33]. A target of 50% free cephalosporin drug concentration greater than the drug MIC (fT > MIC) has been identified as the quantitative exposure necessary for effective cephalosporin bactericidal activity [34]. Monte Carlo simulation is a mathematical tool that may be applied to integrating multiple pharmacokinetic/pharmacodynamic (PK/PD) variables to estimate the probability of target attainment for specific

Table 3. Observational Studies Evaluating Clinical Outcomes of Patients with Extended-Spectrum β-Lactamase Infections Comparing Treatment with Cephamycins versus Carbapenems

Study	Cephamycin	Carbapenem	Organism(s)	ESBL Criteria	Sites and Sources of Infection	Severity of Illness at Infection Onset	Clinical Outcomes (Cephamycins vs Carbapenems)	Select Limitations[a]
Lee et al [15]	Flomoxef (n = 7)	n = 20	*Klebsiella pneumoniae* (100%)	Molecular confirmation	Site: bloodstream (100%) Sources: pneumonia (56%), intra-abdominal (19%), urinary (11%), SSTI (4%)	52% admitted to ICU	Mortality at 14 d: 29% vs 25% (ns[b])	More severely ill patients in carbapenem arm
Doi et al [17]	Cefmetazole (n = 10)	n = 12	*Escherichia coli* (95%), *K. pneumoniae* (5%)	Disk diffusion	Site: urine (100%)	Not provided (but likely low)	Clinical cure at 4 weeks: 90% vs 100% (ns)	More patients in carbapenem group with bacteremia or complicated UTI; 90% of patients in cephamycin group received alternative agents initially
Yang et al [18]	Flomoxef (n = 29)	n = 28	*K. pneumoniae* (100%)	Disk diffusion	Site: bloodstream (100%) Source: fistula, graft, catheter (100%)	51% admitted to ICU	Mortality at 14 days: 55% vs 39% ($P < .05$)	Unclear if removal of infected hardware occurred at similar percentages across the 2 treatment groups
Pilmis et al [19]	Cefoxitin[c] (n = 8)	n = 31	*E. coli* (32%), *K. pneumoniae* (32%), *Enterobacter cloacae* (36%)	Not described	Site: urine (75%), bloodstream (25%)	Not provided	Clinical or microbiological relapse at 30 d: 13% vs 23% (ns)	Patients in carbapenem group more likely to be immunocompromised
Matsumura et al [20]	Empiric: cefmetazole or flomoxef (n = 26) Definitive: cefmetazole or flomoxef (n = 59)	Empiric: n = 45 Definitive: n = 54	*E. coli* (100%)	Disk diffusion	Site: bloodstream (100%) Source: urinary (45%), intra-abdominal (32%)	41% with severe sepsis	Mortality at 30 d in empiric group: 8% vs 9% (ns) Mortality at 30 d in definitive therapy group: 5% vs 9% (ns)	Patients in carbapenem group more ill and more likely to be immunocompromised

Abbreviations: ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; ns, not significant; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

[a]Small sample size, residual confounding, and confounding by indication are limitations for all included studies.

[b]Not statistically significant using a P value ≤.05.

[c]Excluding patients who initially received carbapenems and then converted to cephamycins.

fT > MIC targets. There are a wide range of dosing regimens for cefepime, which may dramatically alter exposure and outcomes associated with treatment. Reese and colleagues showed that 2 g of cefepime every 12 hours was unable to achieve an adequate fT > MIC in a medically complex population in which the cefepime MIC_{50} and MIC_{90} values were 8 μg/mL and 16 μg/mL, respectively [35]. Others have shown similar results [36], prompting the CLSI to implement a susceptible dose-dependent category encouraging cefepime doses of 1 g every 8 hours or 2 g every 8 hours for organisms with MICs of 4 or 8 μg/mL, respectively [22].

The relative contribution of ESBL production and drug MIC towards cefepime efficacy remains controversial. Andes and Craig studied the impact of ESBL production on the activity of cefepime in a neutropenic murine thigh model of infection [37]. ESBL production in 5 isolates had no impact upon the fT > MIC necessary for in vivo cefepime efficacy. Rather, they concluded, cefepime efficacy is predicted exclusively by the contribution of the MIC in relation to the magnitude of drug exposure. However, cefepime failures for ESBL-producing infections have been observed with cefepime MICs as low as 1 μg/mL [38], suggesting that both the presence of ESBLs and higher MICs likely contribute to cefepime failures.

Results of observational studies comparing the activity of cefepime and carbapenems for invasive ESBL infections have been conflicting with some studies showing no difference [39, 40] and others suggesting cefepime therapy is inferior [38, 41, 42] (Table 4). Lee and colleagues conducted an observational study including 17 patients with ESBL bacteremia receiving cefepime therapy and 161 patients receiving carbapenem therapy [42]. Patients receiving carbapenems were over 7 times more likely to survive than patients receiving cefepime. Mortality rates were lower with cefepime MICs ≤1 μg/mL (17%) compared with MICs of 2–8 μg/mL (46%). No patients received cefepime 2 g every 8 hours or continuous infusion cefepime to evaluate how

Table 4. Observational Studies Evaluating Clinical Outcomes of Patients with Extended-Spectrum β-Lactamase Infections Comparing Treatment with Cefepime versus Carbapenems

Study	Cefepime (Dosing if Available)	Carbapenem	Organism(s)	ESBL Criteria	Sites and Sources of Infection	Severity of Illness at Infection Onset	Clinical Outcomes (Cefepime vs Carbapenems)	Select Limitations[a]
Zanetti et al [41]	n = 13; 2 g every 8 h	n = 10	*Klebsiella pneumoniae* (96%), *Enterobacter aerogenes* (4%)	Not provided	Site: pneumonia (100%)	100% admitted to ICU	Clinical response: 69% vs 100% ($P < .05$)	Cefepime MIC distributions not provided; baseline comparisons specifically for ESBL producers not provided
Goethaert et al [39]	n = 21; 2 g every 8 h	n = 23	*E. aerogenes* (100%)	Disk diffusion and molecular confirmation	Sites: pneumonia (64%), bloodstream (16%), urine (5%), intra-abdominal (14%), bone (0.3%)	100% admitted to ICU	Mortality at 30 d: 33% vs 26% (ns)	~80% of patients (equally in both groups) received combination antibiotic therapy; bacteremia more likely in carbapenem group; analysis limited to isolates containing bla_{TEM-24} gene
Chopra et al [40]	Empiric: cefepime monotherapy n = 43 Definitive: cefepime monotherapy n = 9	Empiric: carbapenem monotherapy n = 14 Definitive: carbapenem monotherapy n = 33	*K. pneumoniae* (83%), *Escherichia coli* (17%)	Disk diffusion	Site: bloodstream (100%) Sources: catheter (75%)	41% admitted to ICU	In-hospital mortality for empirical group: 40% vs 36% (ns) In-hospital mortality for definitive group: 33% vs 36% (ns)	Cefepime dosing not described; baseline comparisons of patients receiving cefepime vs carbapenems not provided
Lee et al [42]	Empiric: n = 21 Definitive: n = 17 1 g every 8 h (41%) and 2 g every 12 h (47%)	Empiric: n = 91 Definitive: n = 161	*Enterobacter cloacae* (55%), *E. coli* (24%), *K. pneumoniae* (21%)	ESBL Etest strip and molecular confirmation	Site: bloodstream (100%) Sources: pneumonia (24%), catheter (21%), intra-abdominal (16%), skin and soft tissue (6%), urinary (22%)	67% had Pitt bacteremia score ≥4	Mortality at 30 d in definitive therapy group: 59% vs 17% ($P < .01$)	21% of patients receiving cefepime had cefepime MICs >8 μg/mL; propensity score analysis used but no description of variables included in generating propensity score, making residual confounding possible
Wang et al [38]	n = 17; 2 g every 8 h (71%) and 1 g every 8 h (29%)	n = 51	*E. coli* (32%), *Klebsiella* spp (63%), *Proteus mirabilis* (3%)	ESBL Etest strip	Site: bloodstream (100%) Sources: catheter (44%), urinary (31%), biliary (9%), pneumonia 15%), intra-abdominal (13%), skin and soft tissue (3%)	29% admitted to ICU	Mortality at 14 d: 41% vs 20% ($P = .08$)	No patients received continuous-infusion cefepime

Abbreviations: ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; ns, not significant; MIC, minimum inhibitory concentration.

[a]Small sample size, residual confounding, and confounding by indication are limitations for all included studies.

optimizing PK/PD could have impacted outcomes. However, in a study where all ESBL-infected patients received cefepime at 8-hour intervals and 70% of patients received 2 g every 8 hours, inferior outcomes were still observed in the cefepime group [38].

We believe cefepime can be considered for nonsevere ESBL infections where the agent can achieve high concentrations to ensure pharmacodynamic targets are met (eg, urinary tract infections (UTIs) with cefepime MICs ≤2 μg/mL). We do not favor the use of cefepime for serious ESBL infections. If cefepime is administered for nonsevere ESBL-producing infections with MICs of 4–8 μg/mL based on susceptibility criteria, we recommend administering 2 g every 8 hours, possibly as a continuous infusion.

PIPERACILLIN-TAZOBACTAM

Current breakpoints for piperacillin-tazobactam (PTZ) according to the CLSI [22] and EUCAST [23] are ≤16 μg/mL and ≤8 μg/mL, respectively. Despite a considerable proportion of ESBL isolates demonstrating susceptibility to PTZ [43], the role of this compound for patients infected with ESBL-producing pathogens remains unclear. Although ESBLs are generally inhibited by β-lactamase inhibitors, occasionally organisms produce multiple ESBLs simultaneously or have additional resistance mechanisms (eg, AmpC β-lactamases, OMP mutations), providing a complex background that may reduce the effectiveness of these agents [5]. Similar to cefepime, an "inoculum effect" has been proposed. This is supported by in vitro, animal data, and case reports [26, 30, 44–46]. In the time-kill experiments by Burgess and colleagues described above, PTZ maintained >99% killing against high inoculum non-ESBL *K. pneumoniae* isolates over a 24-hour period, but this effect was nonsustainable against high-inoculum ESBL infections, where regrowth was observed at 8 hours [32].

Existing observational data have indicated contradictory results between outcomes of patients receiving PTZ and carbapenems for the treatment of ESBL infections (Table 5) [8, 47, 48–54]. Rodriguez-Baño and colleagues provided some of the earliest robust data evaluating β-lactam–β-lactamase inhibitors (βL-βLIs) and carbapenems for the treatment of ESBL bacteremia by conducting a post hoc observational study of Spanish patients from 6 cohorts [47]. To overcome limitations with antibiotic regimen changes between empiric therapy and definitive therapy regimens, 2 nonmutually exclusive cohorts were constructed and independently analyzed. Thirty-day mortality was 10% and 19% in the empiric cohort and 9% and 17% in the definitive cohort for βL-βLIs and carbapenems, respectively. Although these differences did not reach statistical significance, the absolute difference in mortality being almost twice as high in the carbapenem group gives us pause as to whether some selection bias remained that was not unaccounted for. There were some aspects to this study potentially compromising its generalizability. First, only *E. coli* isolates that typically contained bla_{CTX-M} genes were included. It is unclear if similar outcomes would be observed with *K. pneumoniae* isolates containing bla_{SHV}-type genes. Second, approximately 70% of bloodstream isolates were from urinary and biliary sources (ie, "low-inoculum" infections). It remains undetermined if similar findings would have been observed if the majority of patients had bloodstream infections due to pneumonia or intra-abdominal infections. Third, approximately 13% of patients required intensive care unit (ICU) admission, signifying that most patients were not critically ill. Additionally, the median piperacillin MIC was only 2 μg/mL. Importantly, mortality was 4.5% when the MIC was ≤4 μg/mL vs 23% for an MIC of ≥8 μg/mL. Finally, >90% of patients receiving PTZ were administered 4.5 g every 6 hours. Simulation models have shown a 99% probability of attaining PK/PD targets against ESBL producers with PTZ administered at 4.5 g every 6 hours when MICs are ≤8 μg/mL, compared with a probability of only 57% with piperacillin MICs of 16 μg/mL [55].

A meta-analysis by Vardakas et al compared carbapenem and βL-βLIs for ESBL bacteremia for both empiric use (273 βL-βLIs vs 317 carbapenems) and definitive use (118 βL-βLIs and 398 carbapenems) [6]. There was no difference in all-cause mortality between the empiric and definitive therapies. The meta-analysis was limited by considerable heterogeneity of the studies and because more severely ill patients tended to be prescribed carbapenems (Table 2). Unfortunately, adjustment for potential confounders using patient-level data was not feasible.

As the majority of patients had a urinary source for their bacteremia in the Rodriguez-Baño study, Ofer-Friedman and colleagues compared the efficacy of βL-βLI and carbapenems for the treatment of ESBL bacteremia, excluding urinary sources [8]. Thirty-day mortality was 60% for the PTZ group and 34% for the carbapenem group. These differences did not attain statistical significance ($P = .10$), although it is plausible that this is at least partly due to the restricted sample size. This limitation notwithstanding, this study suggests that for critically ill patients with ESBL bacteremia from nonurinary sources, PTZ therapy may lead to less desirable outcomes than carbapenem therapy.

Tamma et al compared 14-day mortality of patients receiving PTZ and carbapenems as empiric therapy in a cohort of patients with ESBL bacteremia who all received definitive carbapenem therapy [51]. The study population resembled the Ofer-Friedman et al study where about one-third of the isolates were *E. coli*, one-third of patients required ICU care, the majority of patients had "high-inoculum" infections, and most ESBL isolates had elevated PTZ MICs. In fact, 99% of organisms had piperacillin MICs of ≥4 μg/mL, with a median MIC of 8 μg/mL. Thirty-day mortality was higher in the PTZ group (Table 5). It should be noted that in both this study and the Ofer-Friedman et al study, the minority of patients received PTZ dosed at 4.5 g every 6 hours.

More recently, Gutiérrez-Gutiérrez et al conducted a multinational, observational study investigating this question in a design similar to the Rodriguez-Baño study [52]. In fact, some of the same

Table 5. Observational Studies Evaluating Clinical Outcomes of Patients with Extended-Spectrum β-Lactamase Bacteremia Comparing Treatment with β-Lactam–β-Lactamase Inhibitors versus Carbapenems

Study	βL-βLI	Carbapenem	Organism(s)	ESBL Criteria and βL-βLI MIC Distribution, μg/mL	Sources of Bacteremia	ICU Admission at Infection Onset	Clinical Outcomes (βL-βLI vs carbapenems)	Select Limitations[a]
Kang et al [49]	n = 36	n = 78	*Escherichia coli* (68%), *Klebsiella pneumoniae* (32%)	Not provided	Sources: not provided	Not provided	Mortality at 30 d: 22% vs 27% (ns)	Baseline comparisons not provided
Rodriguez-Baño et al [47]	Empiric cohort: n = 72 Definitive cohort: n = 54	Empiric cohort: n = 31 Definitive cohort: n = 120	*E. coli* (100%)	Molecular detection MICs: ≤1 (29%), 2 (23%), 4 (11%), 8 (17%), 16 (20%)	Source: urinary or biliary (70%)	13%	Mortality at 30 d in empiric cohort: 10% vs 19% (ns) Mortality at 30 d in definitive cohort: 9% vs 17% (ns)	Generalizability to patients infected with ESBL bloodstream infections from high-inoculum sources, elevated piperacillin MICs, and severe infections not clear
Harris et al [50]	n = 24 (100% 4.5 g per dose PTZ)	n = 23	*E. coli* (86%) *K. pneumoniae* (14%)	Cefotaxime nonsusceptible MICs: ≤4 (71%) and 8 (29%)	Sources: urinary (47%), biliary (9%)	15%	Mortality at 30 d: 8% vs 17% (ns)	More immunocompromised patients in carbapenem group, generalizability to patients infected with ESBL bloodstream infections from high-inoculum sources, elevated piperacillin MICs, and severe infections not clear
Ofer-Friedman et al [8]	n = 10 (dosing regimens not described)	n = 69	*E. coli* (53%), *K. pneumoniae* (28%), *Proteus mirabilis* (19%)	Disk diffusion MICs: median 8	Sources: pneumonia (34%), skin and soft tissue (28%), biliary (17%), intra-abdominal (9%)	>50%	Mortality at 30 d: 60% vs 34% ($P = .10$) Mortality at 90 d: 80% vs 48% ($P = .03$)	Endpoint of 90-d mortality may not be representative of mortality due to poor antibiotic treatment choices; dosing not described
Tamma et al [51]	n = 103 (40% received 4.5 g per dose PTZ)	n = 110	*K. pneumoniae* (68%), *E. coli* (31%), *P. mirabilis* (1%)	Disk diffusion MICs: 2 (1%), 4 (39%), 8 (46%), 16 (14%)	Sources: catheter (46%), urinary (21%), intra-abdominal (17%) biliary (9%), pneumonia (9%)	34%	Mortality at 14 d: 17% vs 8% ($P < .05$) Mortality at 30 d: 26% vs 11% ($P < .01$)	Only ~40% received 4.5 g every 6 h; no patients received extended-infusion therapy
Ng et al [53]	Empiric cohort: n = 97 (~100% 4.5 g)	Empiric cohort: n = 57	*E. coli* (67%), *K. pneumoniae* (33%)	Resistance to third-generation cephalosporins MICs: not provided	Sources: catheter (4%), urinary (59%), biliary (9%), pneumonia (9%), intra-abdominal (5%)	9%	Mortality at 30 d: 31% vs 30% (ns)	PTZ MIC distribution not provided; unclear what proportion of infections were due to ESBL producers
Gutiérrez-Gutiérrez et al [52]	Empiric cohort: n = 170 (65% received 4.5 g per dose PTZ) Definitive cohort: n = 92 (83% received 4.5 g per dose PTZ)	Empiric cohort: n = 195 Definitive cohort: n = 509	*E. coli* (73%), *K. pneumoniae* (19%)	Elevated cephalosporin MICs with molecular confirmation of ~30% of cohort MICs: not provided	Sources: urinary (45%), biliary (12%)	11%	Mortality at 30 d in empiric cohort: 18% vs 20% (ns) Mortality at 30 d in definitive cohort: 10% vs 14% (ns)	Generalizability to patients infected with ESBL bloodstream infections from high-inoculum sources, elevated piperacillin MICs, and severe infections not clear

Abbreviations: βL-βLI, β-lactam–β-lactamase inhibitor; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; MIC, minimum inhibitory concentration; ns, not significant; PTZ, piperacillin-tazobactam.

[a]Small sample size, residual confounding, and confounding by indication are limitations for all included studies.

patients were included in both cohorts. This has been the largest study to date comparing the effectiveness of βL-βLIs compared with carbapenems for the treatment of ESBL bloodstream infections, including 365 patients in the empiric therapy group and 601 patients in the targeted therapy group. This study was expanded to include patients infected with *K. pneumoniae* isolates, comprising 19% of cases. However, similar to the original study, only 11% of patients required ICU-level care and the majority of isolates were from urinary or biliary sources. Similar to the Rodriguez-Baño study, the vast majority of patients (83%) received 4.5-g PTZ dosing. Mortality was comparable between the study groups in both the empiric and definitive cohorts. The investigators attempted to overcome some of the differences with the Ofer-Friedman et al and Tamma et al studies by conducting a series of subgroup analyses comparing outcomes for patients treated with βL-βLIs and carbapenems (eg, *E. coli* vs *K. pneumoniae* isolates, severe sepsis vs non–severely ill, urinary sources vs other sources). In subgroup analysis, the investigators were able to demonstrate that the point estimates and confidence intervals resembled estimates from the entire cohort. Although the investigators found no differences within the subgroups, it is unknown if this is an artifact of the small sample size within any individual subgroup. An important observation was that patients with ESBL-producing *K. pneumoniae* bloodstream infections had almost twice the odds of dying within 30 days compared to patients with ESBL-producing *E. coli* bacteremia.

Finally, Ng and colleagues evaluated 30-day mortality comparing empiric PTZ and carbapenem in 151 patients with presumed ESBL bloodstream infections. Thirty-day mortality was no different between the groups [53]. As with previous studies that resulted in similar outcomes between the treatment groups, a minority of patients were in the ICU (<10%), the majority of patients were infected with *E. coli* bacteremia, and almost 70% of patients had urinary or biliary sources of bacteremia. Patients in the PTZ group received 4.5-g dosing. Importantly, confirmatory ESBL testing was not conducted, so it is unclear what proportion of ceftriaxone-resistant isolates were indeed ESBL producers.

An important lingering question is as follows: Are the poorer outcomes in the Ofer-Friedman et al and Tamma et al studies related to the suboptimal performance of βL-βLIs for critically ill patients with more aggressive infections (high inoculum, higher median PTZ MICs, greater proportion of *K. pneumoniae* isolates), or are they related to the underdosing of βL-βLIs in both of these studies? Unfortunately, the answer to this question remains unknown. It is not clear if patients receiving βL-βLIs would have had more favorable outcomes had target PK/PD exposures been achieved. Perhaps the discrepancies between these studies will be resolved with the MERINO trial [54], a multicenter, randomized noninferiority trial comparing meropenem 1 g every 8 hours and PTZ 4.5 g every 6 hours for ceftriaxone-nonsusceptible *E. coli* and *Klebsiella* species bloodstream infections (ClinicalTrials.gov identifier NCT02176122).

Unfortunately, the question of whether βL-βLIs and carbapenems lead to equivalent outcomes when prescribed for ESBL infections remains unclear. Based on the experiences of the Rodriguez-Baño, Gutiérrez-Gutiérrez, and Ng studies, βL-βLIs appear to be very reasonable options for low- to moderate-severity infections, infections resulting from urinary or biliary sources, and infections with piperacillin MICs <4 μg/mL. For critically ill patients, patients with higher inoculum infections, and elevated piperacillin MICs, we believe that it might be more appropriate to administer carbapenem therapy, at least initially, until more data are available. Regardless, if PTZ is administered to patients with invasive ESBL infections, we would recommend administering 4.5 g every 6 hours (or 4.5 g every 8 hours as extended infusion) [55].

NEWER B-LACTAM–B-LACTAMASE INHIBITORS

The US Food and Drug Administration recently approved 2 new βL-βLIs, ceftolozane-tazobactam and ceftazidime-avibactam, which are active in vitro against ESBL-producing organisms. Ceftolozane demonstrates good activity against Enterobacteriaceae. Similar to other oxyimino-cephalosporins, its activity is limited against ESBLs. Tazobactam is a potent, irreversible inhibitor of most ESBLs. The MIC_{50}/MIC_{90} of this agent for ESBL-producing *E. coli* and *K. pneumoniae* are 0.5/4 μg/mL and 4/>32 μg/mL, respectively [56, 57]. Differences in MIC distributions may be reflective of discrepancies in ESBL genes present. The $bla_{CTX\text{-}M}$ genes predominate in *E. coli*, whereas there is often a preponderance of $bla_{TEM/SHV}$ in *K. pneumoniae,* with variations in local epidemiology [5].

Ceftolozane-tazobactam (in combination with metronidazole) was compared to meropenem for the treatment of complicated intra-abdominal infections in phase 2 [58] and phase 3 [59] trials that included 4 and 50 people, respectively, with ESBL-producing Enterobacteriaceae. Although the limited number of ESBLs precluded a robust analysis, this compound performed similarly against ESBL-producing and non-ESBL producing isolates.

Ceftazidime-avibactam is usually more active in vitro against ESBL producers than ceftolozane-tazobactam. The MIC_{50}/MIC_{90} of this agent for ESBL-producing *E. coli* and *K. pneumoniae* are 0.12/0.25 μg/mL and 0.5/1 μg/mL, respectively [60]. Similar to ceftolozane-tazobactam, phase 2 [61] and phase 3 studies [62] compared ceftazidime-avibactam (plus metronidazole) vs meropenem for intra-abdominal infections, but did not specifically compare outcomes of ESBL-confirmed pathogens. Data from a phase 3 study comparing ceftazidime-avibactam and doripenem in UTIs showed similar microbiological response for ceftazidime-resistant Enterobacteriaceae, most of which were ESBL producers [63]. Although evidence thus far suggests a potential role for these new cephalosporin/β-lactamase inhibitor antibiotics against ESBL-producing organisms, clinical data remain limited. Additionally, the significant expense of utilizing these new cephalosporin/β-lactamase inhibitor agents is a limiting factor when alternative, less costly options are available.

CONCLUSIONS

Utilizing noncarbapenem β-lactams for the treatment of ESBL-producing organisms is an effective strategy to reduce carbapenem utilization and the associated downstream effects of carbapenem overuse. Available data suggest that cephamycins, cefepime, and βL-βLIs are potential alternatives for frequently encountered ESBL clinical scenarios such as patients with mild to moderate "low-inoculum" infections, with the most robust data available for βL-βLIs. On the other hand, carbapenems are still preferred, at least initially, for critically ill patients, infections with a high bacterial load, or elevated β-lactam MICs until more definitive data become available.

Notes

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