

Extended-Spectrum β -Lactamases and Clinical Outcomes: Current Data

Reuben Ramphal¹ and Paul G. Ambrose²

¹Departments of Medicine, Microbiology, and Molecular Genetics, University of Florida Health Sciences Center, Gainesville; and ²Institute for Clinical Pharmacodynamics at Ordway Research, Albany, New York

Nosocomial infections caused by extended-spectrum β -lactamase (ESBL)-producing gram-negative bacteria complicate therapy and limit treatment options. However, the clinical significance of infections caused by ESBL-producing bacteria remains unclear. A critical examination of the literature provides divergent views of the effect of ESBL carriage on morbidity and mortality and suggests that ESBL production may have its most marked effect on ceftazidime. Effective strategies for the empirical and directed treatment of infections caused by ESBL-producing pathogens include the use of carbapenems and, possibly, the fourth-generation cephalosporin cefepime. Studies indicate that the use of cefepime to treat serious nosocomial infections (e.g., bacteremia, pneumonia, and urinary tract infections) is associated with high rates of microbiological and clinical success. The probability of attaining time above the minimum inhibitory concentration targets of at least 70% of the dosing interval, an important pharmacodynamic indicator of clinical success, is higher with cefepime than with other antimicrobials against *Escherichia coli* and *Klebsiella pneumoniae* strains exhibiting ESBL phenotypes. However, for non-ESBL-producing strains, there is no difference in the time above the minimum inhibitory concentration between ceftazidime and cefepime. When used appropriately in institutional settings, cefepime reduces the overall use of cephalosporins, thereby decreasing selection pressure for presumptive ESBL-producing pathogens.

Infections caused by multidrug-resistant bacteria expressing extended-spectrum β -lactamases (ESBLs) pose serious challenges to clinicians. Because ESBL-producing bacteria are resistant to a broad range of β -lactams, including third-generation cephalosporins, nosocomial infections caused by these organisms complicate therapy and limit treatment options [1]. In addition, patients infected with ESBL-producing bacteria may have a higher mortality rate and may require longer hospital stays because they are generally sicker and have received more antibiotics than patients who are not infected with ESBL-producing strains. Nevertheless, the clinical significance of infections caused by ESBL-producing bacteria remains unclear, primarily because few prospective studies have been designed specifically to evaluate clin-

ical outcomes among a statistically meaningful number of patients [2, 3]. Studies of this kind are essential for developing consensus guidelines (which are not currently available) for the treatment of infection due to ESBL-producing bacilli.

A critical examination of the literature provides divergent views of the role of ESBL carriage in death and suggests that ESBL production may have its most marked effect on ceftazidime, but this could be a geographic or enzyme-specific variation [3, 4]. The present review summarizes recent reports in the medical literature related to the clinical significance of ESBL expression and describes strategies for the treatment of infections caused by ESBL-producing pathogens. Among those strategies is the use of cefepime, a fourth-generation cephalosporin with greater stability than third-generation cephalosporins against many ESBL-producing bacteria. The literature on the use of cefepime against ESBL-producing pathogens is limited, and there is controversy regarding whether this agent or,

Reprints and correspondence: Dr. Reuben Ramphal, Depts. of Medicine, Microbiology, and Molecular Genetics, University of Florida Health Sciences Center, 1600 SW Archer Rd., Rm. R2-130, Gainesville, FL 32610 (ramphr@medmac.ufl.edu).

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for that matter, any cephalosporin should be used against these organisms. The latest clinical and experimental data on the activity of cefepime against such pathogens are reviewed here.

ASSESSING THE CLINICAL SIGNIFICANCE OF ESBL PRODUCTION BY NOSOCOMIAL PATHOGENS

Although the occurrence of ESBL-producing organisms has been extensively reported in the literature since the early 1980s, the clinical significance of ESBL production has received comparatively little attention. Even among the few studies that address the issue, the question of whether ESBL production significantly increases the risk of death—or any other measurement of clinical failure—remains unresolved.

Table 1 [2, 3, 5–13] summarizes the divergent results of studies that have attempted to determine whether ESBL production by infecting organisms has a demonstrable effect on clinical outcomes. A number of studies found no significant association between ESBL production and treatment failure or crude mortality [5–10]. In contrast, several other studies observed that patients with infection due to ESBL-producing bacilli tended to have poorer outcomes than did comparable patients with infection caused by pathogens that did not produce ESBLs [11–13].

Studies have indicated that choosing an appropriate therapy soon after the onset of infection is an important factor in determining outcome. Du et al. [5], who did not find an association between ESBL status and outcome, nevertheless reported that ESBL production in *Escherichia coli* and *Klebsiella pneumoniae* bacteremia was more likely to lead to the choice of inappropriate empirical therapy, which, in turn, increased the risk of treatment failure or death. In contrast, Ariffin et al. [11] found that overall sepsis-related mortality was significantly higher among patients infected with ceftazidime-resistant *K. pneumoniae* (50.0%) than among patients infected with ceftazidime-susceptible *K. pneumoniae* (13.3%). They also reported that, for patients who did not receive antibiotics directed toward ceftazidime-resistant infection within 48 h of admission, the risk of a fatal outcome was significantly higher than that for patients who received timely and appropriate therapy [11]. Not all studies have found that inappropriate empirical therapy administered prior to the availability of culture results always leads to a poor outcome. In a study of 162 cases of *K. pneumoniae* bacteremia, which concluded that ESBL production was not significantly associated with mortality, there were 19 cases of infection with ESBL-producing *K. pneumoniae* for which no significant difference in mortality was observed among patients who received appropriate empirical therapy, compared with those who did not [9]. However, the average hospital stay was significantly longer for patients with infection due to ESBL-

producing *K. pneumoniae* than for patients with infection due to non-ESBL-producing *K. pneumoniae* [9].

It is apparent from table 1 that there is also disagreement with regard to the role of third-generation cephalosporin treatment in outcomes. A study of bloodstream infections caused by ESBL-producing *E. coli* and *K. pneumoniae* in children found no difference in the clinical severity of infection between patients infected with ESBL-producing and non-ESBL-producing strains, yet the overall mortality rate among patients infected with ESBL-producing strains was ~4 times greater than that of the patients infected with non-ESBL-producing strains [12]. A subset of patients was analyzed for their response to therapy with a third-generation cephalosporin, administered with or without an aminoglycoside, to which the infecting pathogen appeared to be susceptible (as determined by in vitro testing). Nevertheless, mortality was considerably higher among patients infected with ESBL-producing strains than among patients infected with non-ESBL-producing strains (24% vs. 2%, respectively), and, at the end of therapy, the favorable response rate was ~53% among patients infected with ESBL-producing strains who received cephalosporin therapy and 94% among patients infected with non-ESBL-producing strains [12]. In contrast, Du et al. [5] found no overall difference in mortality among patients infected with ESBL-producing versus non-ESBL-producing strains. Surprisingly, they also reported higher mortality among patients infected with non-ESBL-producing strains who were treated with third-generation cephalosporins (36%) than in similarly treated patients infected with ESBL-producing organisms (28%) [5].

CLINICAL OUTCOMES AND ESBL PRODUCTION: INTERPRETING THE DATA

The aforementioned discordant results concerning the clinical significance of ESBL production might be due to a number of factors. First, most of the existing studies are underpowered. The nature and clinical severity of the underlying disease at the time antimicrobial therapy was initiated are other factors. A study by Wong-Beringer et al. [3] suggests that the choice of cephalosporin used for empirical therapy may also have an important effect on outcome. The investigators concluded that, for infections caused by ESBL-producing pathogens, failure of treatment with cephalosporins might occur at higher rates with ceftazidime than with other third-generation cephalosporins. They assessed treatment outcomes for 36 cases of bloodstream infection caused by ceftazidime-resistant strains of *E. coli* and *K. pneumoniae* that produced 5 types of ESBLs: TEM-12, TEM-71, TEM-6, SHV-12, and SHV-5 [3]. In most cases, initial empirical treatment was with ceftazidime or ceftizoxime. For bacteremias caused by ESBL-producing strains, no significant difference in treatment response was observed between regimens that included a cephalosporin and those that did not.

Table 1. Outcomes for patients treated for bacteremia caused by extended-spectrum β -lactamase (ESBL)-producing organisms: selected retrospective studies.

Type of study, reference	ESBL strain	Type of infection	ESBL status	Antibiotic-specific mortality	Outcome (mortality or failure)	Notes
Noncomparative studies						
Paterson et al. [2]	<i>Klebsiella pneumoniae</i>	Bacteremia	Positive (n = 10)	All patients were treated with 3GCs and 4GCs: CTZ (n = 2), ceftriaxone (n = 4), and other (n = 4).	7 of 10 patients experienced failure, and 4 of 10 died	Isolates were apparently susceptible to the 3GC or 4GC used; failure was defined as death within 14 days of first positive culture or continued fever
Wong-Beringer et al. [3]	<i>Escherichia coli</i> and <i>K. pneumoniae</i>	Bacteremia	Positive (n = 36)	...	5 (14%) of 36 patients died, and 7 (19%) and 36 experienced failure	AmpC and TEM/SHV-type ESBLs; CTZ failed in all patients
Comparative studies finding no effect of ESBL status on outcomes						
Du [5]	<i>E. coli</i> and <i>K. pneumoniae</i>	Bacteremia	Positive (n = 23)	2 (28%) of 7 patients given 3GC died	26% of patients experienced failure, and 13% of patients died	...
			Negative (n = 62)	12 (36%) of 33 patients given 3GC died	27% of patients experienced failure, and 29% of patients died	...
Schiappa et al. [6]	<i>E. coli</i> and <i>K. pneumoniae</i>	Bacteremia	...	19 of 31 patients with CTZ-R strains received appropriate therapy; of these, 1 (5%) died; 12 received inappropriate therapy, and 5 (42%) died	6 (19%) of 31 patients died	CTZ resistance due to TEM-10
Yoon et al. [7]	<i>K. pneumoniae</i>	Bacteremia	Positive (n = 41)	All-cause mortality rate was not significantly different for ESBL-negative and -positive groups
			Negative (n = 82)
Chemaly et al. [8] ^a	<i>K. pneumoniae</i>	Bacteremia	Positive (n = 24)	...	29% died	87% of ESBL-positive group were not receiving antibiotics to which the ESBL-producing <i>K. pneumoniae</i> had in vitro susceptibility at the onset of bacteremia
Kim et al. [9]	<i>K. pneumoniae</i>	Bacteremia	Negative (n = 50)	...	12% died	...
			Positive (n = 44)	...	23% died ^b	In ESBL-positive group, there was no significant difference in mortality between patients who received appropriate empirical therapy and those who did not
Emery et al. [10]	Various Enterobacteriaceae	UTI, sepsis, and others	Negative (n = 118)	...	20% died ^b	...
			Positive	2 (22%) of 9 patients treated with a 3GC died	26% crude mortality rate; ^b 17% mortality rate (minus those who died with a cured infection)	Mortality rate in patients treated with 3GC was similar to the overall mortality rate
Comparative studies finding important effects of ESBL status on outcomes						
Ariffin et al. [11]	<i>K. pneumoniae</i>	Bacteremia in children with febrile neutropenia	8 (50%) of 16 patients with CTZ-R strains died ^c ; 2 (13.3%) of 15 patients with CTZ-S strains died ^d	Antibiotic treatment not specified; empirical therapy consisted of CTZ plus amikacin
			Positive (n = 45)	4 (23%) of 17 patients given ES Ceph died	12 (27%) of 45 patients died ^a	ES Ceph was effective against infecting organism by in vitro testing
Kim et al. [12]	<i>E. coli</i> and <i>K. pneumoniae</i>	Bacteremia in children	Negative (n = 87)	1 (2%) of 50 patients given ES Ceph died	5 (6%) of 87 patients died ^a	...
Ho et al. [13]	<i>E. coli</i>	Bacteremia	Positive (n = 50)	3 (43%) of 7 patients given empirical CTZ (MIC ≤8 µg/mL) died	9 (18%) of 50 patients died ^a	Empirical therapy was with CTZ
			Negative (n = 100)	...	7 (7%) of 100 patients died ^a	...

NOTE. 3GC, third-generation cephalosporin; 4GC, fourth-generation cephalosporin; CTZ, ceftazidime; CTZ-R, CTZ-resistant; CTZ-S, CTZ-susceptible; ES Ceph, extended-spectrum cephalosporin; UTI, urinary tract infection.

^a Nonsignificant difference.

^b Significant difference.

With noncephalosporin regimens, there was a trend toward better outcomes that did not reach statistical significance. Although ceftazidime treatment was always associated with treatment failure, a favorable response to treatment with a third-generation cephalosporin other than ceftazidime was observed for cases in which the ESBL was identified as TEM-6 or TEM-12; these 2 ESBLs have relatively weaker hydrolytic activity against extended-spectrum cephalosporins. The authors of that study, however, recommend that use of an extended-spectrum cephalosporin for treatment of a confirmed ESBL-producing organism be avoided.

Other examples of favorable responses after switching from ceftazidime to another third-generation cephalosporin have been reported in cases of putative infection with organisms that produce TEM-type ESBLs. During an outbreak of ceftazidime-resistant *K. pneumoniae* in a long-term care facility, a different third-generation cephalosporin, cefotaxime, proved to be effective in 4 patients [14]. However, it should be noted that the number of cases was relatively small. In a similar report [15], a patient with bacteremia and meningitis due to an ESBL-producing strain of *K. pneumoniae* experienced treatment failure with ceftazidime and amikacin but improved and recovered after treatment was switched to cefotaxime plus amikacin.

Data from in vitro studies of the differential activities of third-generation cephalosporins against ESBL-producing bacilli of known phenotypes would appear to support some of the observed clinical differences. For example, *K. pneumoniae* isolates expressing the TEM-10 type of ESBL were resistant to ceftazidime and aztreonam but were susceptible to other cephalosporins [16]. For *E. coli* isolates that produce the cefotaxime-hydrolyzing-14 β -lactamase, in vitro tests indicated resistance to cefotaxime but susceptibility to ceftazidime [17]. TEM-71, an ESBL produced by a *K. pneumoniae* clinical isolate, exhibited a substrate profile in which hydrolysis of cefotaxime was preferred over ceftazidime [18]. Recognizing the variability in substrate preferences among the ESBLs, the NCCLS standards were amended in 1999 to recommend use of an expanded number of cephalosporin substrates during screening and confirmatory testing [19].

The relatively low level of accuracy in testing for ESBLs reported for many clinical laboratories suggests that clinical failures might be occurring at higher rates in the general population than is perhaps indicated by published clinical studies. In a study of ESBL-mediated resistance in 220 *Klebsiella* species isolates recovered from 35 intensive care units in Europe, communicating laboratories incorrectly reported the susceptibilities of a large proportion of isolates. In the pooled analysis, 28.9% of the ESBL-producing isolates tested were reported to be susceptible to ceftriaxone, and 36.6% were reported to be susceptible to cefotaxime [20]. A discrepancy of this magnitude is disturbing, because even low levels of in vitro resistance can

be associated with clinical failure. Such an occurrence was reported by Brun-Buisson et al. [21] during a nosocomial outbreak of multidrug-resistant *K. pneumoniae*. The isolates exhibited a mode MIC for cefotaxime of 2 mg/L, indicating a low level of resistance. Although a regimen that included cefotaxime or ceftriaxone proved to be effective in treating cases of uncomplicated urinary tract infection, these antimicrobials failed to treat major infections at other sites.

A related problem posed by ESBL-producing organisms—one that might differentially affect outcomes—is that treatment failure can occur even when the infection appears to be susceptible to the chosen antibiotic. This fact was demonstrated by Paterson et al. [2] in a prospective study of 10 patients who received treatment for bacteremia caused by ESBL-producing *K. pneumoniae*. In all cases, in vitro tests indicated that the infecting strains were not resistant to the utilized cephalosporin (i.e., ceftazidime, ceftriaxone, cefotaxime, or cefepime), yet treatment failure was recorded for 7 of the patients. The definition of failure in that study may have been too broad in terms of clinical evaluation (i.e., fever for >48 h or death within 2 weeks, rather than death attributable to the infection), given that patients dying of gram-negative bacteremia rapidly succumb to septic shock. A supplemental review of published outcomes for 36 cases of bacteremia found that clinical failure occurred in all 4 cases in which the MIC values of the cephalosporin used for treatment were in the intermediate range; clinical failure even occurred in 54% of cases for which the MIC of the cephalosporin used for treatment was in the susceptible range [2].

An inoculum effect, in which the MIC increases with increasing inoculum, has been proposed as a possible explanation for treatment failure occurring in the face of apparent in vitro susceptibility. Diminished efficacy at higher inocula has been reported in association with the use of the β -lactam antimicrobial agents cefotaxime and ceftriaxone for the treatment of ESBL-producing pathogens. However, the contribution of this effect toward treatment failures has not been the subject of comprehensive clinical study [22, 23].

The inoculum effect has more recently been shown to be an artifact of in vitro susceptibility methodology that is not of clinical significance. When susceptibility testing is performed on ESBL-producing organisms, the initial bacterial killing results in the release of additional β -lactamase into the test system and consequent hydrolysis of the antimicrobial agent. At a higher inoculum, a greater number of bacterial cells are killed, releasing additional β -lactamase into the test system where no new drug is introduced; thus, the MIC value increases [24]. In animal infection models, the time above the MIC ($T > MIC$) required for efficacy has been demonstrated to be essentially the same for ESBL-producing and non-ESBL-producing strains [25, 26]. This insight is critical, because it suggests that it is

not ESBL production that is predictive of efficacy, but rather the MIC value of the predictive outcome. In other words, if a given dosing regimen attains the $T > \text{MIC}$ target, then the probability of a positive clinical outcome occurring is not affected by ESBL production. Therefore, the correct question may be this: given a standard dosing regimen and $T > \text{MIC}$ target, what is the highest MIC value that can be covered? Analyses of pharmacokinetic/pharmacodynamic target attainment suggest that the susceptibility breakpoints for Enterobacteriaceae and intravenously administered cephalosporins are too high, often by $>2 \log_2$ dilutions [27]. The Clinical Laboratory Standards Institute, formerly known as the NCCLS, is currently reevaluating cephalosporin susceptibility breakpoints for Enterobacteriaceae.

TREATMENT FOR INFECTION WITH ESBL-PRODUCING ORGANISMS

Carbapenems. On the basis of a survey of the relevant clinical literature by Wong-Beringer [4], the carbapenems, especially imipenem, have demonstrated a relatively high rate of clinical success among patients infected with ESBL-producing *E. coli* or *K. pneumoniae*. Of 80 patients who received treatment with an imipenem-containing regimen, all but 3 had a favorable response or were cured.

The use of a carbapenem may be associated with a low risk of mortality in cases of serious infection caused by ESBL-producing pathogens. In a retrospective study of consecutive patients, those treated with imipenem for nosocomial bloodstream infection due to ESBL-producing *E. coli* or *K. pneumoniae* were significantly more likely to survive than were such patients treated with a cephalosporin [5]. In fact, previous treatment with a third-generation cephalosporin was determined to be the sole independent risk factor for bloodstream infection caused by ESBL-producing organisms. This observation led the investigators to conclude that more cautious use of third-generation cephalosporins might be important for decreasing ESBL-producing *E. coli* or *K. pneumoniae* bacteremia and improving outcomes.

The carbapenems have been used successfully to control outbreaks of infection due to ESBL-producing pathogens. In one such occurrence, the incidence of ceftazidime-resistant *K. pneumoniae* at a single hospital reached a peak of 17.3% of all *Klebsiella* isolates, with 155 patients becoming colonized or infected [28]. The outbreak, which was attributed to production of TEM-type ESBLs by *K. pneumoniae* [28], occurred at a time when ceftazidime was being used in increased amounts to control multiresistant *Acinetobacter* infections. The most effective treatment regimens were ones that included imipenem [28].

Epidemiological and surveillance studies have found that the carbapenems remain highly active against cephalosporin-resistant gram-negative bacteria [29, 30]. The Meropenem Yearly Susceptibility Test Information Collection surveillance program

reported that, from 1997 through 2000, meropenem and imipenem were highly active against important species of gram-negative isolates from European intensive care units and were much more active than ceftazidime; the difference is likely to reflect, at least in part, the presence of ESBL-producing strains [31]. In the United States, Pfaller et al. [32] surveyed 10–15 Meropenem Yearly Susceptibility Test Information Collection Program centers during 1999 through 2000. The carbapenems showed consistently high activity against all ESBL-producing strains of *E. coli* and *Klebsiella* species [32].

Piperacillin-tazobactam. Piperacillin-tazobactam contains a semisynthetic penicillin in combination with the β -lactamase inhibitor tazobactam. To date, no prospective randomized trials have examined the efficacy of piperacillin-tazobactam in patients with ESBL-producing pathogens, but several case studies and surveillance studies suggest that the agent may have a role in treating this type of infection.

The SENTRY Antimicrobial Surveillance Program examined 2773 organisms recovered from patients with pneumonia who were treated at 30 hospitals in the United States and Canada during the 1998 respiratory illness season [33]. ESBL phenotypes were identified among *Klebsiella* isolates from 5 US medical centers, which translated into an overall frequency of 4.8%–6.0%, relative to the entire sampled population. In vitro testing demonstrated that $>90\%$ of the ESBL-producing isolates were susceptible to piperacillin-tazobactam, a rate that was similar to the rates noted for cefepime, imipenem, meropenem, aminoglycosides, and fluoroquinolones. By comparison, only 77.6% and 79.6% of ESBL-producing *Klebsiella* strains were susceptible to ceftazidime and cefotaxime, respectively [33]. Another study examined the in vitro activity of a broad array of antibacterials, including piperacillin-tazobactam, against clinical isolates from a single tertiary hospital in Brazil [34]. Overall, $\sim 20\%$ of the *E. coli* and $\sim 40\%$ of the *K. pneumoniae* isolates produced ESBLs. Piperacillin-tazobactam was the second most active antibacterial, after imipenem, against these ESBL-producing pathogens, inhibiting 84.4% of the isolates [34].

One small, retrospective clinical study compared the efficacy of piperacillin-tazobactam with those of other antibacterials in neonates during an outbreak of nosocomial *K. pneumoniae* infection [35]. Among the 33 neonates in the study, 13 were treated with piperacillin-tazobactam, 17 with imipenem-cilastatin, 2 with cefotaxime, and 1 with ciprofloxacin. Eighteen (54.5%) of the isolates recovered from the neonates produced ESBL. Six (35.3%) of the 17 neonates treated with imipenem died, compared with 6 (46.2%) of 13 neonates treated with piperacillin-tazobactam. Moreover, the duration of antimicrobial therapy and the total duration of hospitalization were similar for the latter 2 groups [35].

The existing data suggest that piperacillin-tazobactam may

be a useful agent for the treatment of some infections with ESBL-producing pathogens. At the present time, however, this potential recommendation must be interpreted cautiously, because it is based on a relatively small database of information. Definitive conclusions regarding the efficacy of piperacillin-tazobactam for ESBL infections must await large-scale, prospective, randomized clinical trials.

Aminoglycosides. Aminoglycosides show variable activities against Enterobacteriaceae that produce ESBLs. However, there is a marked increase in resistance to aminoglycosides when non-ESBL-producing *E. coli* and *Klebsiella* species are compared with strains that produce ESBLs, with the risk of resistance to aminoglycosides increasing by 2–3-fold [36]. Among aminoglycosides, amikacin is likely to show the greatest percentage of susceptible strains, particularly in the United States [37]. With resistance rates of ~10% in the United States, amikacin is a likely alternative for empirical therapy when other agents cannot be used, but there are no published clinical data on monotherapy with this agent that would confidently support this contention. However, the success of aminoglycosides in general against bacteremias caused by ESBL-producing *K. pneumoniae* has been well demonstrated [12]. Whether or not strains produced ESBLs, if the ratio of the MIC for the infecting strain to the breakpoint of the aminoglycoside was $\leq 1:8$, the clinical success rate was ~90%–100%, whereas, if this ratio was lower, the clinical success rate was 14%. Because this observation was not restricted to ESBL-producing strains, it is simply a demonstration of how the efficacy of aminoglycoside is concentration dependent. Thus, the limited amount of data suggests that efficacy is good when the aminoglycoside has a low MIC against the infecting strain.

Fluoroquinolones. Quinolone antibiotics have shown limited success in treating infections caused by ESBL-producing pathogens. Rice et al. [14] reported using ciprofloxacin to successfully treat a number of infections caused by ceftazidime-resistant Enterobacteriaceae. Ciprofloxacin was also reported to be effective in treating a patient infected with ESBL-producing *K. pneumoniae* for whom treatment with cefotaxime failed [22]. In a septic mouse model of infection with *K. pneumoniae* expressing the SHV-5 ESBL, fluoroquinolones significantly prolonged survival [38]. Fluoroquinolones are particularly useful for the treatment of urinary tract infections, because high concentrations in the urine can be achieved [39]. In a study of urinary tract isolates that included ESBL-producing strains, all *E. coli* isolates proved to be susceptible to levofloxacin [39]. Furthermore, in a 1997 study of ESBL-producing *K. pneumoniae* isolates recovered from hospitals in Brazil, a 94% susceptibility rate to ciprofloxacin was observed [40].

Increased coresistance to fluoroquinolones has, however, begun to undermine the effectiveness of fluoroquinolones against ESBL-producing pathogens. A multicenter prospective study of

K. pneumoniae bloodstream infection conducted in 7 countries found that 18% of ESBL-producing isolates were ciprofloxacin resistant as well, and that 78% of ciprofloxacin-resistant *K. pneumoniae* isolates that caused nosocomial bacteremia produced ESBL [41].

Regional studies have confirmed the emergence of fluoroquinolone coresistance in ESBL-producing organisms. In a nationwide Italian survey, among ESBL-producing strains of Enterobacteriaceae, only 58% were susceptible to ciprofloxacin [42]. Rates of ciprofloxacin resistance are reported to be very high among presumptive ESBL-producing isolates collected from Asian centers [43]. In Taiwan, concomitant ciprofloxacin resistance was observed in almost 20% of ESBL-producing *K. pneumoniae* isolates [44]. In the United States, outbreaks of coresistant organisms have occurred. In 1999, a cluster of 15 hospitals in Brooklyn, New York, reported that 34% of *K. pneumoniae* isolates were presumptive ESBL producers, and, of these, only 42% were susceptible to ciprofloxacin [45]. Risk factors identified for fluoroquinolone resistance in ESBL-producing *E. coli* and *K. pneumoniae* infections included fluoroquinolone use, aminoglycoside use, and residence in a long-term care facility [46].

Cefepime. Cefepime is a fourth-generation cephalosporin that is more stable than third-generation cephalosporins against some ESBLs and very stable against AmpC-type β -lactamases. In vitro studies have confirmed that ESBL-producing organisms are generally susceptible to the antimicrobial action of cefepime [40, 47], suggesting that cefepime may be of clinical value for the treatment of some infections caused by bacterial strains that are resistant to third-generation cephalosporins. In addition to its in vitro activity, the pharmacokinetic/pharmacodynamic properties of cefepime appear to contribute to and support its bactericidal activity [48].

Because it is a composite of susceptibility and pharmacokinetic data, $T > \text{MIC}$ is a valuable predictor of in vivo activity for β -lactams [49]. Ambrose et al. [49] estimated the probability of attaining $T > \text{MIC}$ targets, ranging from 30% to 70% of the dosing interval, by use of standard dosing regimens of both piperacillin-tazobactam and cefepime against *E. coli* and *K. pneumoniae* strains exhibiting ESBL phenotypes. For cefepime regimens, doses were administered twice daily, whereas doses of piperacillin-tazobactam were administered every 4 or 6 h. The probability of meeting a $T > \text{MIC}$ target of 50%–60% with cefepime was determined to be equal to or higher than that with piperacillin-tazobactam, regardless of which dosing regimen was modeled or which microorganism was considered [49]. For ESBL-producing *K. pneumoniae*, the difference in probabilities especially favored cefepime regimens over those of the β -lactam/ β -lactamase inhibitor combination [49]. Because $T > \text{MIC}$ of 50%–60% of the dosing interval is likely to produce nearly optimal antimicrobial activity, the data suggest

that standard dosing regimens of cefepime are likely to have clinical efficacy [48].

A number of clinical reports have described the successful use of cefepime in the treatment of infections caused by ESBL-producing organisms (table 2) [50–52]. In a report of 43 critically ill patients with infections caused by ESBL-producing *Enterobacter aerogenes*, no significant differences in outcomes were observed between carbapenem- and cefepime-treated patients [50]. Clinical improvement was seen in 69.6% of patients receiving a carbapenem, compared with 61.9% of those receiving cefepime ($P = .752$), and bacteriological eradication was achieved in 21.7% of patients receiving carbapenem, compared with 14% of patients receiving cefepime ($P = .762$). Mortality rates were 33.3% for the patients receiving cefepime, compared with 21.7% for the patients receiving carbapenem ($P = .437$). In a study of 44 patients with infections caused by ESBL-producing strains of *E. coli* and *Klebsiella* species, bacteriological eradication with cefepime therapy was achieved in 80% (24/30) of cases in which isolates proved to be susceptible to cefepime in vitro (MIC, $\leq 8 \mu\text{g/mL}$); more than one-third of in vitro-resistant isolates were eradicated with cefepime [51]. In a comparison study of imipenem versus cefepime for the treatment of nosocomial pneumonia, bacteriological eradication rates for a subset of patients with nosocomial pneumonia due to ESBL-producing organisms were 83% and 70% for cefepime and imipenem, respectively. A randomized trial compared cefepime (2 g thrice daily) with imipenem-cilastatin (500 mg once daily) for the treatment of nosocomial pneumonia in 281 intensive care unit patients [52]. The clinical response rates for pneumonia caused by an ESBL-producing organism were

69% (9 of 13 patients) in the cefepime group and 100% (10 of 10 patients) in the imipenem group. Although cefepime was less active against ESBL-producing organisms, primary and secondary resistance to imipenem was more common for *Pseudomonas aeruginosa*. It should, however, be noted that, in the United States, the recommended dose for cefepime for nosocomial pneumonias is 1–2 g twice daily.

When used appropriately in institutional settings, cefepime, along with a reduction of the overall use of third-generation cephalosporins, has resulted in a lower prevalence of presumptive ESBL-producing pathogens. This was the conclusion derived from a study of antimicrobial resistance patterns before and after a university hospital formulary change [53]. During the formulary change, cefepime was substituted for ceftazidime and cefotaxime. Combined use of the third-generation cephalosporins decreased by almost 90%, whereas cefepime use increased dramatically during the same period. The formulary change was associated with significant changes in infections possibly caused by ESBL-producing bacteria. The rate of infection due to ceftazidime-resistant *K. pneumoniae* decreased from 13% to 3%, and that due to ceftazidime-resistant *P. aeruginosa* decreased from 25% to 15%.

Another benefit of empirical therapy with cefepime might be to preserve the activity of carbapenems in centers that seek to limit the development of resistant pathogens by restricting the use of third-generation cephalosporins. Rahal et al. [54] reported their experience with class restriction of cephalosporins to control an outbreak of cephalosporin-resistant *Klebsiella* species. A hospital-wide reduction in the incidence of ceftazidime-resistant *Klebsiella* species was associated with a reduction

Table 2. Clinical studies of cefepime for the treatment of infections caused by extended-spectrum β -lactamase (ESBL)-producing pathogens.

ESBL-producing strain (type or location of infection), treatment (no. of cases)	Bacteriologic eradication, %	Clinical outcome	Mortality rate, %
<i>Enterobacter aerogenes</i> ^a (pneumonia and sepsis)			
Cefepime ($n = 21$)	14.3	61.9% improvement	33.3
Carbapenem ($n = 23$)	21.7	69.6% improvement	26.1
Not specified (nosocomial pneumonia)			
Cefepime ($n = 13$)	...	69% cure and improvement	...
Imipenem ($n = 10$)	...	100% cure and improvement	...
<i>Escherichia coli</i> and <i>Klebsiella</i> spp. (various sites)			
Cefepime ^b susceptible ^c ($n = 30$)	24 (80) ^d
Cefepime resistant ^c ($n = 14$)	5 (37.5) ^d	90% cure for UTI, 76% cure for LRTI, and 45% cure for bacteremia	...
<i>E. coli</i> and <i>Klebsiella</i> spp. (pneumonia)			
Cefepime ($n = 12$)	83
Imipenem ($n = 12$)	70

NOTE. Data are from [50–52]. LRTI, lower respiratory tract infection; UTI, urinary tract infection.

^a Difference between treatment groups was not significant.

^b Empirical therapy.

^c Cases for which isolates tested susceptible or resistant in vitro.

^d Data are no. (%) of cases.

in cephalosporin use and an increase in imipenem use [54]. However, a significant increase in the incidence of imipenem-resistant *P. aeruginosa* occurred throughout the medical center, confirming the need for judicious use of carbapenems to reduce the risk of selection for resistant organisms.

CONCLUSIONS

Because ESBL-producing strains are resistant to a wide range of β -lactams, including third-generation cephalosporins, outbreaks complicate treatment decisions and limit therapy options. Looking beyond these implications, studies have detailed the economic impact of the nosocomial outbreaks and treatment failures, such as significantly longer hospital stays and increased hospital charges [55, 56]. In an effort to improve the management of infections caused by ESBL-producing strains, this *Clinical Infectious Diseases* supplement issue has put forth the merits of various treatment strategies, including the use of carbapenems and fluorquinolones. Special attention was given to the use of cefepime, because recent data suggest that it is a potentially valuable addition to current alternatives for the empirical treatment of multidrug-resistant infections. Moving forward, these documented studies and currently emerging data should be utilized to more clearly determine the clinical significance of infections caused by ESBL-producing bacteria and to develop consensus guidelines to improve management efforts.

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