MAJOR ARTICLE

Antibiotic Therapy for *Klebsiella pneumoniae* Bacteremia: Implications of Production of Extended-Spectrum β-Lactamases

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The prevalence of extended-spectrum β-lactamase (ESBL) production by *Klebsiella pneumonia* approaches 50% in some countries, with particularly high rates in eastern Europe and Latin America. No randomized trials have ever been performed on treatment of bacteremia due to ESBL-producing organisms; existing data comes only from retrospective, single-institution studies. In a prospective study of 455 consecutive episodes of *Klebsiella pneumoniae* bacteremia in 12 hospitals in 7 countries, 85 episodes were due to an ESBL–producing organism. Failure to use an antibiotic active against ESBL-producing *K. pneumoniae* was associated with extremely high mortality. Use of a carbapenem (primarily imipenem) was associated with a significantly lower 14-day mortality than was use of other antibiotics active in vitro. Multivariate analysis including other predictors of mortality showed that use of a carbapenem during the 5-day period after onset of bacteremia due to an ESBL-producing organism was independently associated with lower mortality. Antibiotic choice is particularly important in seriously ill patients with infections due to ESBL-producing *K. pneumoniae*.

Since their description in the mid-1980s, extended-spectrum β-lactamase (ESBL)–producing organisms have become recognized as a worldwide problem [1]. ESBL-producing organisms have been detected in every inhabited continent [2]. Although ESBLs have been detected in a wide variety of gram-negative bacteria, *Klebsiella pneumoniae* has been found to be the most common species to produce ESBLs [1]. In the United States, between January 1998 and June 2002, 6.1% of *K. pneumoniae* isolates from patients in the intensive care unit (ICU) of hospitals participating in the National Nosocomial Infections Surveillance (NNIS) system were nonsusceptible to third-generation cephalosporins or aztreonam [3]. In 10% of NNIS ICUs, at least 27% of all isolates were nonsusceptible to third-generation cephalosporins or aztreonam [3]. (This definition is neither entirely sensitive nor specific for ESBL production but serves as a surrogate marker for production of this type of β-lactamase.)

ESBL-producing organisms may be more common in some parts of Europe, Asia, and South America than in the United States [2, 4, 5]. In a 1997–1998 survey of *Klebsiella* isolates from ICUs in southern and western Europe, 25% possessed ESBLs [6]. However, in a 2000 survey of eastern European centers (e.g., Russia, Poland, and Turkey), almost 50% of *K. pneumoniae* isolates produced ESBLs [7]. Similarly high rates of ESBL production have been observed in some parts of Asia and Central and South America [5].

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Despite the high prevalence of ESBL-producing organisms in many parts of the world, data on the treatment of serious infections due to such organisms remain sparse. To our knowledge, no randomized controlled trials have ever been performed that evaluated the use of various comparator antibiotics in the treatment of serious infections due to ESBL-producing organisms. For a variety of practical reasons, it is unlikely that such a study will ever be performed. In the absence of data from randomized controlled trials, the objective of this report is to describe experience with various agents in the treatment of serious infections due to ESBL-producing organisms. This experience has been derived from the largest prospective study of *K. pneumoniae* bacteremia ever performed [8, 9].

PATIENTS AND METHODS

Study design. A prospective, observational study of consecutive, sequentially encountered patients with *K. pneumoniae* bacteremia was performed in 12 hospitals in South Africa, Taiwan, Australia, Argentina, the United States, Belgium, and Turkey. The study design has been described in detail elsewhere [8]. The study period was 1 January 1996 to 31 December 1997. Patients aged >6 years with blood cultures positive for *K. pneumoniae* were enrolled, and a 188-item study form was completed. Patients were observed for 1 month after the first positive blood culture result to assess clinical outcome, including mortality and infectious complications. The study was observational in that administration of antimicrobial agents and performance of other therapeutic management was at the discretion of the patient's physician, not the investigators. The study was approved by institutional review boards, as required by the policies of participating hospitals at the time of the study.

Definitions. Definitions were defined a priori (that is, before data analysis). Nosocomial bacteremia was defined as bacteremia occurring >48 h after admission to the hospital. Severity-of-illness scores included the APACHE III score (for patients in an ICU at the time of onset of bacteremia) [10] and the Pitt bacteremia score [11–13]. The Pitt bacteremia score was calculated using the following criteria: (1) oral temperature: 2 points for a temperature of ≤35°C or ≥40°C, 1 point for a temperature of 35.1–36.0°C or 39.0–39.9°C, and 0 points for a temperature of 36.1–38.9°C; (2) hypotension: 2 points for an acute hypotensive event with decreases in systolic and diastolic blood pressure of >30 and >20 mm Hg, respectively, use of intravenous vasopressor agents, or systolic blood pressure <90 mm Hg; (3) receipt of mechanical ventilation: 2 points; (4) cardiac arrest: 4 points; and (5) mental status: alert, 0 points; disoriented, 1 point; stuporous, 2 points; and comatose, 4 points. Immunocompromise was defined as presence of neutropenia or HIV infection, or receipt of prednisone, cyclosporine, or other iatrogenic immunosuppressive agents. Significant underlying disease was defined as a medical history of diabetes mellitus, chronic liver disease, chronic renal failure, HIV infection, malignancy, solid-organ transplantation, or serious burns. Types of infection were determined to be pneumonia, urinary tract infection, meningitis, incisional wound infection, other soft-tissue infections, intraabdominal infection, or primary bloodstream infection, according to Centers for Disease Control and Prevention definitions [14].

Antibiotic therapy for the episode of *K. pneumoniae* bacteremia comprised agents active in vitro against the blood culture isolate (i.e., the isolate was susceptible to antibiotics, according to 1999 NCCLS breakpoints) [15] that were administered for at least 2 days during the 5-day period after the first positive blood culture result. Monotherapy involved administration of only 1 antibiotic with in vitro activity against the infecting isolate for at least 2 days during this period. Combination therapy for the episode of *K. pneumoniae* bacteremia involved concomitant administration of ≥2 antibiotics, all of which were active in vitro against the infecting isolate, for at least 2 days during the 5-day period after the first positive blood culture result. Patients who received different active antibiotics nonconcurrently during the 5-day period after the first positive blood culture result were defined as having received sequential monotherapy. Patients who survived for >2 days after the first positive culture result and did not receive any antibiotic with in vitro activity against the blood culture isolate for at least 2 days during the 5-day period after the first positive blood culture result were defined as having received no active antibiotic therapy.

The primary end point of the study was death from any cause within 14 days after the date of the first blood culture positive for *K. pneumoniae.* Mortality was also assessed as being probably or definitely due to *K. pneumoniae* bacteremia, the diagnosis of which was made by the patient's physician. This was not used as the primary end point of the study because of the potential for bias in this assessment. A secondary end point was defined as death during the 28-day period after the first blood culture positive for *K. pneumoniae.* Superinfecting bacteremia was defined as the isolation of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* species, *Acinetobacter* species, *Stenotrophomonas maltophilia, Serratia marcescens, Pseudomonas aeruginosa, Enterobacter* species, *Citrobacter* species, or *Candida* species from blood cultures during the 28-day period after the initial blood culture positive for *K. pneumoniae.* Other superinfections were those in which any of the above organisms were isolated from ≥2 nonblood sites or from the same nonblood site on ≥2 occasions during the 28-day period after the first positive blood cultures for *K. pneumoniae.*

Microbiological analysis. ESBL production was pheno-

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typically determined by broth dilution, in accordance with NCCLS performance standards that were current as of January 1999 [15]. A ⩾3 two-fold concentration decrease in MICs of cefotaxime–clavulanic acid and ceftazidime–clavulanic acid, compared with MICs when the 2 agents were tested alone, was considered to be phenotypic confirmation of ESBL production. MICs of antibiotics commonly used in the treatment of sepsis due to gram-negative bacteria were determined for the ESBL-producing isolates by the gradient diffusion method (Etest; AB Biodisk).

Statistical analysis. Patient demographic characteristics and laboratory data were entered into the Prophet Statistics computer program, version 6.0 (AbTech) [16]. The χ^2 test or Fisher's exact test were used to compare categorical variables (e.g., the presence or absence of an underlying condition). Continuous variables (e.g., age) were compared using Student's *t* test or the Mann-Whitney *U* test. A logistic regression model was used to estimate the effects of multiple factors associated with mortality. The logistic model was developed by entering all variables that had *P* values ⩽.2 in the univariate analyses into the initial model. Variables were then eliminated one at a time. The model was clustered on the patient to adjust for multiple episodes. The preliminary model was then tested for possible interactions between the main effects. There were no significant interactions. Estimated ORs and 95% CIs were obtained from this model.

RESULTS

A total of 455 episodes of *K. pneumoniae* bacteremia occurred in 440 patients during the study period; 85 episodes (18.7%) were due to ESBL-producing organisms. A total of 20 (23.5%) of 85 episodes of bacteremia due to ESBL-producing *K. pneumoniae* resulted in death within 14 days after the first positive blood culture result. Three of these deaths were on the day of or the day after blood samples were cultured. These patients are excluded from analysis of antibiotic use and outcome. Failure to treat with any antibiotic with in vitro activity against isolates recovered during the 5-day period after the positive blood culture result was associated with a significantly higher mortality rate (7 [63.6%] of 11 patients) than was treatment with active antibiotics (10 [14.1%] of 71 patients) (OR, 10.7; 95% CI, 2.2–57.0; $P = .001$).

Predictors of mortality associated with ESBL-producing* K. pneumoniae *bacteremia. For patients who received an antibiotic active in vitro against the ESBL-producing *K. pneumoniae* strains, factors significantly associated with death due to ESBL-producing *K. pneumoniae* bacteremia by univariate analysis included accommodation in an ICU at the time of bacteremia (OR, 6.1; 95% CI, 1.4–26.8; $P = .0109$) and increased severity of illness, as determined by the Pitt bacteremia score (OR, 1.5; 95% CI, 1.1–2.0; $P = .006$). Severity of illness, as adjudged by the APACHE III score, was not statistically

Table 1. Comparison of variables between patients with *Klebsiella pneumoniae* bacteremia treated with carbapenems and those treated with other active antibiotics.

Variable	Carbapenem group ($n = 42$)	Noncarbapenem group ($n = 29$)	*P*	OR (95% CI)
Male sex	28 (66.7)	14/29 (48.3)	.15	2.1 (0.7–6.4)
Underlying disease				
Neutropenia	3 (7.1)	0 (0)	.27	…
Any immunocompromise	24 (57.1)	7/29 (24.1)	.006	4.19 (1.3–14.0)
Renal failure	11 (27.5)[a]	10 (35.7)[b]	.47	0.68 (0.2–2.2)
Any significant underlying disease	33 (78.6)	21 (72.4)	.55	1.39 (0.4–4.8)
Underlying source of infection				
Pneumonia	9 (21.4)	7 (24.1)	.79	0.86 (0.2–3.0)
Intra-abdominal infection	6 (14.3)	10 (34.5)	.08	0.31 (0.1–1.1)
Urinary tract infection	8 (19.0)	2 (6.9)	.18	3.2 (0.1–15.4)
Wound infection	4 (9.5)	1 (3.4)	.64	2.9 (0.3–25.8)
Other source	7 (16.7)	2 (6.9)	.29	2.7 (0.5–13.5)
Severity-of-illness marker				
Admission to ICU	15 (35.7)	13 (44.8)	.47	0.7 (0.2–2.0)
APACHE III score, mean ± SD	71.7 ± 16	59.2 ± 23	.16	1.03 (0.98–1.08)
Previous LOS, median days	11.5	15.0	.16	0.99 (0.98–1.01)

NOTE. Data are no. of patients/no. for whom data were available (%), unless otherwise indicated. ICU, intensive care unit; LOS, length of stay.

[a] Data are for 40 patients.

[b] Data are for 28 patients.

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associated with mortality, most probably because it was only used in 24 patients.

Duration of previous hospitalization, transfer from a nursing home, source of infection, presence of underlying diabetes mellitus, chronic liver disease, renal failure, malignancy, neutropenia, or burns, transplantation, recent surgery, and receipt of corticosteroid therapy were not associated with significantly increased mortality ($P > .20$ for all factors).

Antibiotic use and outcome associated with ESBL-producing* K. pneumoniae *bacteremia. Forty-nine episodes of bacteremia due to ESBL-producing *K. pneumoniae* were treated with monotherapy active in vitro (carbapenems were used in 27 cases; ciprofloxacin was used in 11; cephalosporins were used in 5; β-lactam/β-lactamase inhibitor combinations were used in 4; and amikacin was used in 2), 15 were treated with combination therapy (10 combinations involved carbapenems, and 5 did not involve carbapenems), 7 were treated with sequential monotherapy (5 included a carbapenem), and 11 were treated with antibiotics without in vitro activity against the patient's isolate.

Use of a carbapenem (primarily imipenem) was associated with a significantly lower 14-day mortality due to ESBL-producing *K. pneumoniae* bacteremia than was use of other active antibiotics. Patients who received a carbapenem as monotherapy or combination therapy in the 5-day period after the first blood culture positive for *K. pneumoniae* had a significantly lower 14-day all-cause mortality (2 [4.8%] of 42 patients) than did those who received noncarbapenem antibiotics (8 [27.6%] of 29 patients) (OR, 0.173; 95% CI, 0.039–0.755; $P = .012$).

There were no statistically significant differences between any of the variables among patients treated with carbapenems or other active antimicrobial agents, except that patients who received carbapenems were more likely to be immunocompromised (table 1). There were also trends toward higher APACHE III scores for patients who received carbapenems, although this difference was not statistically significant.

Multivariate analysis was performed using variables (primarily severity-of-illness markers) that were determined to be associated with all-cause death at 14 days after the first positive blood culture result by univariate analysis (table 2). In multivariate analysis, we used the following variables: carbapenem use during the 5-day period after the first blood culture positive for *K. pneumoniae,* accommodation in an ICU at the time of bacteremia, and severity of illness (as measured by the Pitt bacteremia score). Carbapenem use was independently associated with decreased mortality (OR, 0.09; 95% CI, 0.01–0.65; $P = .017$) (table 3). Three additional multivariate analyses, which used variables found on univariate analysis to be associated with 28-day all-cause mortality and 14- and 28-day mortality thought to be due to *K. pneumoniae* bacteremia, also showed that carbapenem use was independently associated with decreased mortality (table 3).

Overall, 1 (3.7%) of 27 patients who received carbapenems as the only active antibiotic during the 5-day period after the first positive blood culture result died within 14 days (table 4). The efficacy of carbapenem monotherapy was significantly superior to that of quinolone (mortality, 36.4%; OR, 0.067; 95% CI, 0.001–0.892; $P = .019$) or noncarbapenem β-lactams (mortality, 44.4%; OR, 0.048; 95% CI, 0.0009–0.688; $P = .009$).

One of 10 patients treated with carbapenems in combination with other active antibiotics (4 patients received amikacin, 4

Table 2. Variables revealed by univariate analysis to be associated with all-cause 14-day mortality among patients with *Klebsiella pneumoniae* bacteremia.

Variable	Mortality group ($n = 10$)	Survival group ($n = 61$)	P	OR (95% CI)
Pitt bacteremia score[a]	4.7 ± 2.2	2.1 ± 2.3	.006	1.5 (1.1–2.0)
ICU admission	8 (80)	20 (33)	.0109	6.1 (1.4–26.8)
Carbapenem treatment	2 (20)	40 (66)	.0121	0.2 (0.04–0.8)
Rigor	1 (10)	25 (41)	.081	0.2 (0.02–1.4)
Significant underlying disease	6 (60)	48 (79)	.24	0.5 (0.2–1.5)
Previous LOS	16.6 ± 16.4	36.6 ± 50.9	.24	0.98 (0.96–1.01)
Urinary tract infection	0 (0)	10 (16)	.337	…
Renal failure	4 (40)	17 (29)[b]	.485	1.5 (0.47–4.7)
Previous LOS >14 days	4 (40)	30 (49)	.737	0.7 (0.2–2.3)
APACHE III score[c]	64.5 ± 24	65.8 ± 20	.898	0.99 (0.95–1.04)
Immunocompromise	4 (40)	27 (44)	.99	0.9 (0.3–2.8)

NOTE. Data are no. (%) of patients or mean values ± SD. ICU, intensive care unit; LOS, length of hospital stay.

[a] For a description, see Patients and Methods.

[b] Data are for 58 patients.

[c] Available for only 24 episodes.

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Table 3. Results of multivariate analyses examining risk factors for mortality associated with bacteremia due to extended-spectrum β-lactamase–producing *Klebsiella pneumoniae*.

Mortality risk factor, by time after positive blood culture results	*P*	OR (95% CI)
14-Day mortality		
All cause		
Carbapenem treatment	.017	0.09 (0.01–0.65)
Pitt bacteremia score	.073	1.42 (0.97–2.08)
Admission to ICU	.23	3.46 (0.46–26.26)
Attributed to *K. pneumoniae* bacteremia[a]		
Carbapenem treatment	.013	0.04 (0.002–0.50)
Pitt bacteremia score	.095	1.45 (0.94–2.26)
Admission to ICU	.32	2.89 (0.35–23.90)
28-Day mortality		
All cause		
Admission to ICU	.005	6.90 (1.78–26.69)
LOS before bacteremia	.013	0.97 (0.94–0.99)
Carbapenem treatment	.050	0.28 (0.08–1.00)
Attributed to *K. pneumoniae* bacteremia[a]		
Carbapenem treatment	.001	0.06 (0.01–0.33)
LOS before bacteremia	.019	0.97 (0.94–0.99)
Admission to ICU	.085	4.18 (0.82–21.31)

NOTE. ICU, intensive care unit; LOS, length of hospital stay.

[a] As determined by the treating physicians.

received ciprofloxacin, and 2 received amikacin-ciprofloxacin) died with 14 days after the positive blood culture result. None of 5 patients treated with other combinations of active therapy died (2 patients received ciprofloxacin-amikacin, 2 received ciprofloxacin-gentamicin, and 1 received ceftazidime-tobramycin). There was no statistically significant advantage associated with receipt of ciprofloxacin in combination with drugs from another antibiotic class (1 of 10 patients who received such combination therapy died), compared with receipt of ciprofloxacin alone (4 of 11 patients who received ciprofloxacin only died) ($P = .311$).

Of the 65 patients who survived for at least 14 days after the onset of ESBL-producing *K. pneumoniae* bacteremia, 9 (22.5%) of 40 treated with a carbapenem and 4 (16.0%) of 25 treated with a noncarbapenem had a superinfection with a carbapenem-resistant organism ($P = .75$). A total of 5 (12.5%) of 40 patients who received a carbapenem developed superinfectious bacteremia with a multidrug-resistant organism 15–28 days after the first positive blood culture result (MRSA was recovered from 2 patients, carbapenem-resistant *P. aeruginosa* was recovered from 1, *S. maltophilia* was recovered from 1, and carbapenem-susceptible *Enterobacter cloacae* was recovered from 1), compared with 3 (12.0%) of 25 who did not receive a carbapenem (*Candida albicans* was recovered from 1 patient, MRSA was recovered from 1, and carbapenem-susceptible *P. aeruginosa* was recovered from 1). An additional 5 patients treated with a carbapenem and 2 patients treated with a noncarbapenem developed superinfections, none of which resulted in bacteremia. These infections involved *S. maltophilia* and MRSA in 2 and 3 carbapenem-treated patients, respectively, and *S. maltophilia* and carbapenem-susceptible *Acinetobacter baumannii* in 1 patient each among those who did not receive a carbapenem.

DISCUSSION

Treatment of serious infection with ESBL-producing *K. pneumoniae* is difficult because the organisms are frequently resistant to multiple antibiotics. However, in vitro, ESBL-producing organisms may sometimes appear to be susceptible to combination therapy with β-lactams/β-lactamase inhibitors, third- and fourth-generation cephalosporins, aminoglycosides, and quinolones. Susceptibility rates for these antibiotics are 0%–80%, depending on the geographical location of the study site [5–7]. Carbapenems are stable in the presence of hydrolytic effects of ESBLs, which may explain the consistent finding that >98% of ESBL-producing organisms retain susceptibility to either imipenem or meropenem [5–7]. In our study, all ESBL-producing bloodstream isolates were susceptible to imipenem or meropenem, but 47.2% were resistant to piperacillin-tazobactam, 70.8% were resistant to gentamicin, and 19.4% were resistant to ciprofloxacin.

Potentially, the inferior outcome associated with apparently active cephalosporins and β-lactam/β-lactamase inhibitors, compared with that for other antibiotic classes, could be explained by the inoculum effect. This effect (in which MICs of a drug increase up to 100-fold in the presence of increased inocula) is consistently observed with cefotaxime, ceftriaxone, and cefepime against ESBL-producing organisms [17]. An inoculum effect is least frequently observed with carbapenems; piperacillin-tazobactam has an inoculum effect intermediate between those of carbapenems and cephalosporins [17]. In the 2 patients in this series who died after receiving cephalosporin monotherapy, in vitro MICs increased from 8 μg/mL to >256 μg/mL (for ceftriaxone) and from 0.5 μg/mL to 8 μg/mL (for cefepime) when a 10-fold increase in the inoculum was used. Animal studies also demonstrate an inoculum effect and adverse outcomes when cephalosporins are used to treat ESBL-producing organisms with MICs of cephalosporin in the susceptible range [18–21]. Apart from the inoculum effect, an alternative explanation for failure of β-lactam antibiotics is failure to achieve pharmacodynamic targets.

Quinolones are not prone to substantially increase their MICs against ESBL-producing strains as the inoculum increases. The relatively poor outcome for patients treated with quinolones in this study is possibly the result of underdosing

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Table 4. Antibiotic choice and mortality associated with bacteremia due to extended-spectrum β-lactamase–producing *Klebsiella pneumoniae.*

Type of therapy	All-cause 14-day mortality
Carbapenem monotherapy	1/27 (3.7)
Imipenem	1/24
Meropenem	0/3
Quinolone monotherapy (ciprofloxacin)	4/11 (36.3)
Cephalosporin monotherapy	2/5 (40)
Cefepime	1/2
Ceftriaxone	1/2
Cefotaxime	0/1
β-Lactam/β-lactamase inhbitor combination	2/4 (50)
Piperacillin-tazobactam	2/2
Ticarcillin-clavulanate	0/2
Aminoglycoside monotherapy (amikacin)	0/2 (0)
No active antibiotics	7/11 (63.6)

NOTE. Data are no. of patients who died/no. of patients who received therapy (%). Antibiotic monotherapy is defined as receipt of a single antibiotic, administered for at least 2 days during the 5-day period after the first blood culture positive for *K. pneumonia,* with in vitro activity against the patient's isolate. An additional 7 patients received sequential monotherapy. Mortality associated with concurrent combinations of active antibiotics was as follows: imipenem/amikacin, 0 of 4 patients; imipenem/ciprofloxacin, 0 of 4; imipenem/amikacin/ciprofloxacin, 1 of 2; gentamicin/ciprofloxacin, 0 of 2; amikacin/ciprofloxacin, 0 of 2; and ceftazidime/tobramycin, 0 of 1.

and subsequent failure to reach pharmacodynamic targets correlated with quinolone efficacy. We can only speculate on this, because we did not record drug doses in this study. Although quinolone resistance is widely believed to be the result of mutations in chromosomal genes coding for targets of quinolone action (*gyrA* and *parC*), frequent coexistence of ESBL production and quinolone resistance has been noted [8, 22]. The reasons for this are so far unexplained beyond the potential coexposure of gastrointestinal tract organisms in hospitalized patients to both quinolones and third-generation cephalosporins. Although we found that no patient died who received aminoglycoside monotherapy, because only 2 patients received this therapy, we are therefore reluctant to recommend aminoglycoside monotherapy as a treatment option.

Previous anecdotal reports from single institutions have suggested that carbapenem use may be associated with good clinical outcome in patients with severe infections due to ESBL-producing organisms. In a 1993 report from New York City, Meyer et al. [23, p. 355] noted that "treatment regimens that included imipenem, in contrast to other antibiotics, yielded the most favorable results," although they did not provide specific numbers of patients treated. In a report of an outbreak of infection with ESBL-producing organisms in a pediatric hospital, Bingen et al. [24] found that infections in all 17 patients treated with imipenem were cured. In a study of 21 patients infected with ESBL-producing organisms, Burgess et al. [25] found that all patients treated with carbapenems experienced clinical cure; the only treatment failures were observed in patients who had been treated with piperacillin-tazobactam or cefepime, either alone or in combination with a quinolone. In discussions involving 1–4 patients, a variety of other authors have noted favorable outcomes when carbapenems were used to treat serious infections with ESBL-producing organisms [26–32].

Until now, the only data pertaining to treatment of ESBL-producing organisms have been derived from case reports and small retrospective series. Potential deficiencies of such studies are publication bias, the likelihood that outbreaks of oligoclonal infections involve few ESBL types, and the failure to consider factors such as underlying disease severity and source of infection. We have attempted to address some of these limitations by performing a prospective multicountry study of ESBL-producing organisms in consecutive patients with known disease severity and source of infection. Of course, unforeseen bias may occur in any nonrandomized study with a design similar to ours. Optimally, a large, multicenter, randomized, controlled trial should be performed that compares the efficacy of carbapenems with that of other antibiotic classes. However, at the time of writing, there is no apparent industry or governmental support for such a trial. Until such a trial is performed, we recommend carbapenems as the therapy of choice for treating severe infections with ESBL-producing organisms.

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Conflict of interest. K.P.K. has consulted for Abbott Laboratories, AstraZeneca, Bayer, and GlaxoSmithKline; D.L.P. has consulted for Cubist, Wyeth, Elan, Merck, and AstraZeneca; L.B.R. has consulted for Cubist, Wyeth, Elan, Merck, AstraZeneca, Bristol-Myers Squibb, and Ortho-McNeil Pharmaceuticals; K.P.K. has received honoraria from Abbott Laboratories, AstraZeneca, Bayer, and GlaxoSmithKline; D.L.P. has received honoraria from Wyeth, Merck, AstraZeneca, and Pfizer; and L.B.R. has received honoraria from Elan, Wyeth, Merck, and Ortho-McNeil Pharmaceuticals and has given expert testimony on behalf of Wyeth.

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