MAJOR ARTICLE

β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum β-Lactamase–Producing *Escherichia coli*: A Post Hoc Analysis of Prospective Cohorts

Jesús Rodríguez-Baño,[1,2] María Dolores Navarro,[1] Pilar Retamar,[1] Encarnación Picón,[1] Álvaro Pascual,[1,3] and the Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group[a]

[1]Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, and [2]Departamentos de Medicina and [3]Microbiología, Universidad de Sevilla, Spain

(See the Editorial Commentary by Perez and Bonomo, on pages 175–7.)

Background. Extended-spectrum ß-lactamase–producing *Escherichia coli* (ESBL-EC) is an important cause of invasive infections. Alternatives to carbapenems—considered the drugs of choice—are needed because of the emergence of carbapenemase-producing enterobacteria. The efficacy of ß-lactam/ß-lactam inhibitors (BLBLI) in such infections is controversial.

Methods. The authors performed a post hoc analysis of patients with bloodstream infections due to ESBL-EC from 6 published prospective cohorts. Mortality and length of hospital stay in patients treated with an active BLBLI (amoxicillin-clavulanic acid [AMC] and piperacillin-tazobactam [PTZ]) or carbapenem were compared in 2 cohorts: the empirical therapy cohort (ETC) and the definitive therapy cohort (DTC). Confounding was controlled by multivariate analysis; for patients in the ETC, a propensity score for receiving carbapenem was also used.

Results. The ETC included 103 patients (BLBLI, 72; carbapenem, 31), and the DTC included 174 (BLBLI, 54; carbapenem, 120). Mortality rates at day 30 for those treated with BLBLI versus carbapenems were 9.7% versus 19.4% for the ETC and 9.3% versus 16.7% for the DTC, respectively ($P > .2$, log-rank test). After adjustment for confounders, no association was found between either empirical therapy with BLBLI (adjusted hazard ratio [HR], 1.14; 95% confidence interval [CI], .29–4.40; $P = .84$) or definitive therapy (adjusted HR, 0.76; 95% CI, .28–2.07; $P = .5$) and increased mortality. Furthermore, BLBLI therapy, with respect to carbapenem, was not found to influence length of hospital stay.

Conclusions. These results suggest that AMC and PTZ are suitable alternatives to carbapenems for treating patients with bloodstream infections due to ESBL-EC if active in vitro and would be particularly useful as definitive therapy.

Received 29 May 2011; accepted 19 August 2011; electronically published 4 November 2011.

[a]Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria group members have been listed in the Acknowledgments section.

Correspondence: Jesús Rodríguez-Baño, PhD, MD, Sección de Enfermedades Infecciosas, Hospital Universitario Virgen Macarena, Avda Dr Fedriani 3, 41009 Seville, Spain (jesusrb@us.es).

Clinical Infectious Diseases 2012;54(2):167–74

DOI: 10.1093/cid/cir790

In recent years, the spread of extended-spectrum β-lactamases (ESBLs), particularly CTX-M enzymes, in Enterobacteriaceae has become a serious public health problem worldwide. In fact, ESBL-producing *Escherichia coli* (ESBL-EC) are now a frequent cause of infection in the community and in healthcare centers [1–3]. Carbapenems, which are not affected by ESBLs, are considered the drugs of choice for treating severe infections caused by ESBL producers because, according to some observational studies, the prognosis for patients

Table 1. Characteristics of the 6 Prospective Cohort Studies Providing Patients With Bloodstream Infections Caused by Extended-Spectrum β-Lactamase–Producing *Escherichia coli* for the Present Study

Reference	Participating Centers, No.	Years	Features of Included Patients	No. of Patients		
				Patients in Cohort/Patients With Bacteremia	Patients Included in Post Hoc Analysis: Empirical Therapy	Patients Included in Post Hoc Analysis: Definitive Therapy
13	1	2001–2005	BSI, community and hospital acquired	43/43	19	39
14	11	2002–2003	All types of infections, community onset	122/7	2	4
15	2[a]	2006–2007	All types of infections, community and hospital acquired	80/19	10	15
16	13	2004–2006	BSI, community onset	95/95	30	55
17	13	2004–2006	BSI, hospital acquired	96/96	33	51
9	44	2006	All types of infections, community and nosocomial	304/27	9	10
Total	…	…	…	740/287	103	174

Abbreviation: BSI, blood stream infection.

[a] Only 1 center had eligible patients.

treated with carbapenems is better than for those treated with other drugs, mainly cephalosporins and fluoroquinolones [1–3]. In this context, clinicians are increasingly forced to consider the use of carbapenems as empiric or definitive therapy in moderate or severe community-onset and nosocomial infections whenever an ESBL-producing organism is suspected or demonstrated. This may be leading to an increase in the consumption of carbapenems, which is particularly worrisome in a scenario where carbapenemase-producing organisms are also spreading [4, 5]. Thus, alternatives to carbapenems for the treatment of ESBL producers are urgently needed.

ESBLs are inhibited by β-lactamase inhibitors [1–3]. Although hyperproduction of β-lactamases or additional resistance mechanisms may hamper the activity of these compounds, β-lactam/β-lactam inhibitor combinations (BLBLI) such as amoxicillin-clavulanate (AMC) or piperacillin-tazobactam (PTZ) remain active against a considerable proportion of ESBL-producing enterobacteria, particularly *E. coli,* in many areas [6–10]. However, the efficacy of BLBLI for treating serious infections caused by ESBL-producing enterobacteria is controversial; some authors do not recommend their use [1], but others consider them a useful alternative [11]. PTZ is administered intravenously, whereas AMC may be administered orally or intravenously, although the intravenous formulation is only available in some countries (including Spain but not the United States). This study was conducted to compare the outcomes of patients with bloodstream infections (BSIs) caused by ESBL-EC who had been treated with intravenous BLBLI or carbapenems.

METHODS

Study Design and Patients

This analysis was reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations [12]. We performed a post hoc analysis of individual patients with BSI due to ESBL-EC; these patients had been included in 6 previously published studies carried out in Spain that investigated the epidemiology and clinical impact of ESBL-EC [9, 13–17]. The studies used similar methods: all were prospective cohort studies including all consecutive patients with infections caused by ESBL-producing *E. coli* during each study period in all the participating centers, all used similar questionnaires and definitions for the variables collected, and all were coordinated by our group. No patient was included in >1 cohort. The features of the studies are shown in Table 1.

Patients from these studies were eligible for the present analysis if they fulfilled all of the following criteria: (1) age >17 years; (2) clinically significant monomicrobial bacteremia demonstrated via isolation of ESBL-EC alone in blood cultures, along with criteria for sepsis [18]; and (3) therapy with a BLBLI or a carbapenem for ≥48 hours. Two nonmutually exclusive cohorts were constructed and analyzed separately. The empirical therapy cohort (ETC) included patients who received empirical therapy with BLBLI or carbapenem in monotherapy, whose first dose was administered during the first 24 hours after the blood culture had been drawn and the isolate was susceptible to the empirical antimicrobial administered. The definitive therapy cohort (DTC) included patients receiving definitive monotherapy with an active BLBLI or carbapenem administered for

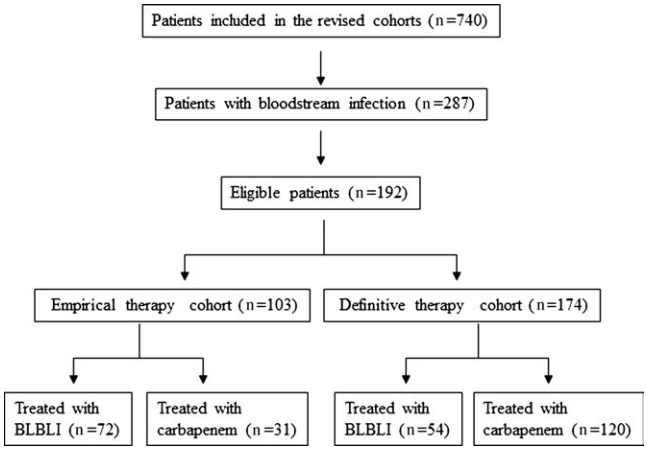

Figure 1. Flow chart of patients included in the study. BLBLI, β-lactam/β-lactamase inhibitor.

≥50% of the total duration of antimicrobial therapy (Figure 1). Data from the previous studies were used and, when necessary, patients' charts were reviewed. Patients were followed up for 30 days. The study was approved by the Ethics Committee of the Hospital Universitario Virgen Macarena, Seville.

The microbiological studies carried out have been published elsewhere [9, 13–17]. In brief, ESBL production and antimicrobial susceptibility were studied according to Clinical and Laboratory Standards Institute recommendations [19, 20]; ESBLs were characterized by polymerase chain reaction and sequencing.

Variables and Definitions

Data collected from all patients included age, sex, nosocomial or community-onset acquisition, type and severity of underlying conditions using the Charlson comorbidity index [21], type of hospital service, source of BSI according to clinical and microbiological data, severity of disease the day before BSI was diagnosed according to Pitt score [22], severity of systemic inflammatory response syndrome at BSI presentation [18], antimicrobial therapy, mortality, and length of stay after BSI.

Antimicrobial therapy administered before susceptibility results were available was considered empirical; therapy administered afterward was considered definitive. Therapy with BLBLI or carbapenem was considered as monotherapy if no other drug with activity against gram-negative organisms—including penicillins, cephalosporins, monobactams, fluoroquinolones, aminoglycosides, trimethoprim-sulphamathoxazole, fosfomycin, or colistin—was coadministered (irrespective of isolate susceptibility). The main outcome variable was mortality; length of hospital stay after BSI was also evaluated.

Statistical Analysis

Separate analyses were performed in the 2 cohorts. Mortality rates of patients treated with BLBLI or carbapenems were compared using Kaplan-Meier curves and log-rank test. Moreover, mortalities at days 7, 14, and 30 were compared using χ^2 test to detect possible trends of very early, early, or late mortality. To control for confounding, multivariate analysis was performed by Cox regression, using time until death as the dependent variable and therapy with BLBLI or carbapenem as the explanatory variable of interest. Potential confounders and interactions were added using a forward method. In the ETC, a propensity score for receiving carbapenem as empirical therapy was added to the model. The propensity score—the probability of receiving carbapenem as empirical therapy—was calculated using a nonparsimonious multivariate logistic regression model in which the outcome variable was use of carbapenem as empirical therapy. The validity of the model was assessed by estimating goodness-of-fit to the data with the Hosmer-Lemeshow test and its discrimination ability with the area under the receiver operating characteristic curve. The software used for the analysis was SPSS (SPSS; version 15.0).

RESULTS

The 6 cohort studies included 740 episodes of infection caused by ESBL-EC, of which 287 were cases of bacteremia. According to the criteria specified in the Methods section, 192 patients were considered eligible for the present study: 103 patients were included in the ETC, 174 were included in the DTC, and 85 were included in both cohorts (Table 1; Figure 1).

Empirical Therapy Cohort

Of the 103 patients included in the ETC, 72 received empirical therapy with a BLBLI (37 AMC, 35 PTZ), and 31 with a carbapenem (imipenem in 22, meropenem in 8, and ertapenem in 1). The characteristics of patients by treatment type are shown in Table 2. The most frequent ESBLs produced by the isolates were CTX-M-14 (50 cases, 48.5%), and CTX-M-15, or SHV-12 (19 cases, 18.4%), with similar distributions for those treated with BLBLI versus carbapenems. Regarding dosage regimens, >90% of patients in each group received the following intravenous doses (or adjusted equivalent in the case of renal failure): PTZ, 4500 mg/6 h; AMC, 1200 g/8 h; imipenem, 500 mg/6 h; meropenem , 1 g/8 h, and ertapenem, 1 g/24 h. Mortality rates among patients treated with BLBLI versus carbapenem were 2.8% versus 9.7% (day 7), 9.7% versus 16.1% (day 14), and 9.7% versus19.4% (day 30), respectively ($P > .1$ by χ^2 test for all comparisons; $P = .2$ by log-rank test). The 30-day mortality rates according to the minimum inhibitory concentrations (MICs) of AMC and PTZ in patients treated with these antibiotics are shown in Table 3; mortality rates were 11.4% (4/35 patients) for those treated with PTZ and 8.1% (3/37 patients) for those treated with AMC ($P = .4$, Fisher test). For patients who received empirical therapy with BLBLI, mortality

Table 2. Characteristics of Patients With Bloodstream Infections (BSIs) Caused by Extended-Spectrum β-Lactamase–Producing *Escherichia coli*, According to Therapy[a]

	Empirical Therapy Cohort			Definitive Therapy Cohort		
Characteristic	BLBLI (n = 72)	Carbapenem (n = 31)	*P*	BLBLI (n = 54)	Carbapenem (n = 120)	*P*
Age, median y (IQR)	69 (59–80)	60 (52–78)	.1[b]	67 (56–83)	70 (55–78)	.3[b]
Male sex	29 (40.3)	11 (35.5)	.6	34 (63)	70 (58.3)	.5
Nosocomial acquisition	26 (36.1)	24 (77.4)	<.001	18 (33.3)	67 (55.8)	.006
Charlson index, median, (IQR)	2 (1–5)	2 (1–5)	.6[b]	2.5 (1–5)	3 (1–5)	.5[b]
Cancer	21 (31.9)	11 (35.5)	.7	15 (27.8)	43 (35.8)	.2
Immunosuppression	5 (6.9)	5 (16.1)	.1[c]	3 (5.6)	15 (12.5)	.1
Neutropenia	2 (2.8)	3 (9.7)	.1[c]	0	7 (5.8)	.1[c]
Urinary or biliary tract as source	52 (72.2)	18 (58.1)	.1	42 (77.8)	79 (65.8)	.1
ICU admission	7 (9.9)	2 (6.7)	.7[c]	4 (7.4)	18 (15.4)	.1
Severe sepsis or shock at presentation	14 (19.4)	9 (29.0)	.2	8 (14.8)	32 (26.7)	.08
Pitt score, median (IQR)	1 (0–2)	1 (0–2)	.7[b]	1 (0–2)	1 (1–2)	.04[b]
CTX-M enzyme	57 (80.3)	25 (86.2)	.4	43 (82.7)	95 (81.2)	.8
Definitive therapy						
Carbapenem	32 (44.4)	30 (93.7)	<.001	…	…	…
BLBLI	34[d] (47.2)	0	<.001	…	…	…
Empirical therapy						
Carbapenem	…	…	…	0	30 (25)	<.001
BLBLI	…	…	…	45[d] (83.3)	38 (31.7)	<.001
Cephalosporins	…	…	…	7 (13)	39 (32.5)	.006
Fluoroquinolones	…	…	…	2 (3.7)	13 (10.8)	.1[c]
Appropriate empirical therapy	…	…	…	34 (63)	64 (53.3)	.2
Mortality, no. of deaths						
Day 7	2 (2.8)	3 (9.7)	.1[c]	1 (1.9)	5 (4.2)	.6[c]
Day 14	7 (9.7)	5 (16.1)	.3	3 (5.6)	14 (11.7)	.2
Day 30	7 (9.7)	6 (19.4)	.1	5 (9.3)	20 (16.7)	.1
Hospital stay after BSI , median (IQR), d	12 (8–28)	13 (9–25)	.7[b]	13 (8–22)	13 (10–25)	.04[b]

[a] Except where otherwise specified, data represent No. (%) of patients. *P* values were calculated by χ^2 test, except where otherwise specified. BLBLI, β-lactam/β-lactamase inhibitor association; ICU, intensive care unit; IQR, interquartile range.

[b] Mann-Whitney test.

[c] Fisher test.

[d] The number of patients empirically treated with BLBLI are different in both cohorts because empirical therapy with these drugs was inappropriate in 11 patients in the Definitive Therapy Cohort, who thus could not be included in the Empirical Therapy Cohort.

at day 30 with respect to definitive therapy was as follows: 5.9% (2/34) for those continuing to receive a BLBLI and 9.4% (3/32) for those whose regimen was changed to a carbapenem ($P = .6$, Fisher test); 2 of 6 patients (33.3%) whose treatment was changed to another antimicrobial died. For patients empirically treated with carbapenems who continued with carbapenem as their definitive therapy, mortality was 16.7% (5/30 patients) ($P > .1$ for comparison with previous groups); 1 patient whose therapy changed to a fluoroquinolone died.

Table 3. Mortality at 30 Days in Patients Who Received Empirical Therapy With an Active β-Lactam/β-Lactam Inhibitor, According to Minimum Inhibitory Concentration of the Antimicrobial Used[a]

	Minimum Inhibitory Concentration, mg/L				
Antimicrobial	≤1	2	4	8	16
Piperacillin-tazobactam	0/10	0/8	1/4	2/6	1/7
Amoxicillin-clavulanate	…	…	1/12	2/25	…

[a] Data are expressed as No. of patients who died/No. of patients treated.

We calculated a propensity score for receiving empirical therapy with a carbapenem by constructing a nonparsimonious model using logistic regression. From the crude comparison results of patients empirically treated with BLBLI and carbapenems (Table 2), the following variables were introduced into the model: age, sex, Charlson index, nosocomial acquisition, Pitt score, neutropenia, cancer, diabetes mellitus, urinary tract disease, chronic renal insufficiency, source, and presentation with severe sepsis or shock. The model showed a *P* value of .53 for the Hosmer-Lemeshow goodness-of-fit test and an area under the receiver operating characteristic curve of 0.80, showing good

Table 4. Cox Regression Analysis of Associations Between Different Variables and Mortality in the Definitive Therapy Cohort

	Crude Analysis		Adjusted Analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Male sex	1.2 (.46–2.29)	.9	…	…
Age[a]	1.00 (.97–1.02)	.9	…	…
Nosocomial BSI	0.99 (.45–2.22)	.9	…	…
Charlson index[a]	1.02 (.88–1.28)	.7	…	…
Neutropenia	1.78 (.88–13.32)	.5	…	…
High-risk source[b]	2.07 (.94–4.54)	.06	…	…
Pitt score[a]	1.49 (1.26–1.78)	<.001	1.38 (1.12–1.70)	.002
Severe sepsis or shock[c]	3.64 (1.66–7.99)	.001	2.10 (.87–5.05)	.09
Empirical therapy with BLBLI	0.56 (.18–1.73)	.3	…	…
Inappropriate empirical therapy	1.76 (.78–3.93)	.1	…	…
Definitive therapy with BLBLI[d]	0.66 (.24–1.76)	.4	0.76 (.28–2.07)	.5

Abbreviations: BLBLI, β-lactam/β-lactamase inhibitor association; BSI, bloodstream infection; CI, confidence interval; HR, hazard ratio.

[a] Per unit.

[b] Other than urinary and biliary tract.

[c] At presentation.

[d] Reference: definitive therapy with carbapenem.

predictive ability. After adjustment for the propensity score in the Cox regression model to evaluate an association with mortality, empirical therapy with BLBLI showed a hazard ratio (HR) of 1.14 (95% confidence interval [CI], .29–4.40; $P = .84$).

Because the crude analysis revealed several variables associated with mortality—namely, source other than biliary or urinary tract, Pitt score, and presentation with severe sepsis or septic shock (data not shown)—several Cox regression models were performed, including propensity score plus combinations of pairs of those variables. Because there were only 13 deaths, a comprehensive model including all variables could not be performed. The adjusted HRs (95% CI) for empirical therapy with BLBLI in the different models ranged from 0.93 (.25–3.51) to 1.27 (.30–5.35), with *P* values between .73 and .93. The inclusion of definitive therapy with BLBLI or carbapenem did not alter the results.

The median postbacteremia hospital stay was 12 days (interquartile range [IQR], 8–27) and 13 days (IQR, 9–22) days for patients who received empirical therapy with BLBLI or carbapenems, respectively ($P = .8$, log-rank test). Empirical therapy with BLBLI with respect to carbapenems showed no association with increased length of stay in survivors after controlling for the propensity score (HR, 1.07; 95% CI, .35–3.02; $P = .9$).

Definitive Therapy Cohort

Overall 174 patients were included in the DTC; 54 received definitive therapy with a BLBLI (36 AMC, 18 PTZ), and 120 received carbapenem (imipenem in 84, meropenem in 16, ertapenem in 20). The dosage regimens were similar to those specified for the ETC. The characteristics of patients by treatment received are shown in Table 2. The most frequent ESBLs produced by the isolates were CTX-M-14 (93 isolates, 53.4%), SHV-12 (16%), and CTX-M-15 (13.7%); there were similar distributions for those treated with BLBLI and carbapenems. Mortality rates for patients receiving definitive therapy with BLBLI versus carbapenem were 1.9% versus 4.2% (day 7), 5.6% versus 11.7% (day 14), and 9.3% vs 16.7% (day 30), respectively ($P > .2$ by χ^2test for all comparisons; $P = .4$ by log-rank test). Ten patients received sequential therapy with oral AMC (none died); the treatment of 4 patients was scaled back from imipenem or meropenem to ertapenem (none died).

Crude analysis showed that source other than urinary or biliary tract, Pitt score, and presentation with severe sepsis or shock were associated with increased mortality. In the multivariate analysis carried out with Cox regression, definitive therapy with BLBLI or carbapenem showed no association with mortality (Table 4). The median hospital stays after bacteremia were 13 days (IQR, 8–22) and 15 days (IQR, 10–25) for patients receiving definitive therapy with BLBLI or carbapenems, respectively ($P = .4$, log-rank test). After controlling for other variables associated with increased length of stay (nosocomial acquisition, source other than urinary or biliary tract, intensive care unit admission, Charlson comorbidity index, and Pitt score), definitive therapy with BLBLI showed no association with increased length of stay in survivors (HR, 1.32; 95% CI, .91–1.90; P=.13).

DISCUSSION

For patients with BSI due to ESBL-EC, this study could not find an association between empirical or definitive therapy using an active BLBLI and increased mortality or length of stay in

comparison with carbapenem therapy. These results suggest that BLBLI, if active in vitro, should be considered a reasonable alternative to carbapenems for treating such infections under certain conditions.

Although the difference was not statistically significant, the fact that crude mortality was higher in patients empirically treated with carbapenems strongly suggests that patients treated with them may have been more severely ill than those treated with BLBLI. We controlled for confounding by calculating a propensity score for receipt of carbapenems as empirical therapy and by performing multivariate analysis using Cox regression. There were no trends that favored the protective effect of carbapenems on mortality or length of stay. We also controlled for potential confounders in the definitive therapy cohort.

Several questions have arisen about the potential efficacy of BLBLI in infections caused by ESBL producers. First, PTZ activity against *E. coli* producing different types of ESBL is significantly reduced in vitro when a high inoculum of bacteria is used [23, 24]. However, a similar effect has been seen with non–ESBL-producing isolates [24], suggesting that the clinical significance of the inoculum effect, if any, would also apply to non–ESBL-producing isolates. It is remarkable that AMC shows no inoculum effect [24].

Second, data from experimental intra-abdominal infection in rats suggested that imipenem was more active than PTZ against TEM-26–producing *Klebsiella pneumoniae* and showed that the response to PTZ might be dose dependent [25, 26]. However, PTZ showed good results against a TEM-3–producing *K. pneumoniae* in an endocarditis model using rabbits [27]. PTZ and AMC, to our knowledge, have not been tested against enterobacteria producing the most frequent ESBLs (namely, CTX-M and SHV enzymes) in animal models.

Finally, Zimhony et al [28] reported treatment failure with PTZ in a patient with prosthetic valve endocarditis caused by CTX-M-2 and OXA-2–producing *K. pneumonia* due to the development of resistance during therapy. We are not aware of other cases in which development of resistance to BLBLI has occurred in vivo. Obviously, ESBL-producing enterobacteria may be BLBLI resistant as a result of additional resistance mechanisms, such as hyperproduction of TEM-1 or SHV-1, production of OXA-1 (frequent in the *E. coli* clonal group ST 131 CTX-M-15 producer [29]), or porin loss (which may also affect carbapenems). Pitout et al reported that the Vitek automated system may fail to detect PTZ resistance, particularly in the case of CTX-M-15– and OXA-1–producing *E. coli*, and recommended using alternative susceptibility testing methods [30].

After reviewing other published series that specify outcome data for patients with BSI due to ESBL-producing enterobacteria and empirically treated with active BLBLI and carbapenems [13, 16, 31–39], we found that 17 of 106 patients treated with BBLBI died, compared with ad 14 of 138 treated with carbapenem died (16% vs 10%; $P = .1$). It is difficult to draw any conclusion from these studies because of the heterogeneous nature of the microorganisms, definitions of mortality, and patient types included; furthermore, BLBLI doses were frequently not specified. If only BSIs caused by *E. coli* are taken into account, the mortality of those treated with BLBLI was 2.7% (1 of 36 patients). The lower rate may be partly due to the fact that the MICs of PTZ and AMC against ESBL-producing ESBL-EC are frequently lower than against other enterobacteria [9, 10], as discussed below. We have reported elsewhere high cure rates for patients with cystitis treated with AMC [14].

One question of interest is the MIC of the isolates and the BLBLI dosage. Stochastic models have shown a 99% probability of attaining the pharmacokinetic/pharmacodynamic target (time above the MIC, >50%) against ESBL producers by using 4500 mg/6 h when the MIC of the isolate is ≤8 mg/L, compared with a probability of only 57% when the MIC is 16 mg/L [40]. Our results also showed increased mortality for higher MICs of PTZ. A higher pharmacokinetic/pharmacodynamic target has been shown with PTZ using more frequent dosing (3375 mg/4 h) or extended infusions [41, 42]. In this regard, the dose used was rarely specified in previous studies. In many countries, the usual dose for PTZ is 3375 mg every 6 to 8 hours, whereas the most frequent dosing in our study was 4500 mg/6 h. There are no similar studies for AMC, although our data would suggest that 1200 mg/8 h, with each dose administered over a 1-hour period, is adequate for most patients.

In deciding whether BLBLI can be used as empirical monotherapy, the susceptibility of local isolates to these compounds should be taken into account. Recent data showed susceptibility prevalences to PTZ in ESBL-EC ranging from 62% to 87% in different areas of the world; the data for ESBL-producing *K. pneumoniae* ranged from 26% to 47% [6, 8]. In a recent nationwide study in Spain, 69% of ESBL-EC isolates were susceptible to AMC [9]; however, most of the isolates are resistant to ampicillin-sulbactam. We do not think that these data support BLBLI use as monotherapy for severe infections potentially caused by ESBL-EC; we do, however, think that our results suggest that PTZ or AMC are suitable options for definitive therapy once the susceptibility results are known, thus providing an opportunity for using a carbapenem-spare regimen. In this way, carbapenem therapy could be scaled back to therapy with an active BLBLI, and any inadequate empirical therapy could be replaced with an active BLBLI instead of a carbapenem.

Some limitations of our study should be considered when interpreting the results. First, this is not a randomized study, and confounding due to unmeasured variables may have occurred. Randomized trials for comparing empirical regimens are difficult to perform in this setting but would be desirable for

comparing definitive treatments. Second, we integrated patients drawn from different cohorts, although the methods used in the different cohorts were very similar. Third, although this is, to our knowledge, the largest series published, its statistical power is limited. Finally, our results are applicable only to BSIs due to ESBL-EC, particularly ESBL-EC originating in the urinary and biliary tracts, the infection source of two-thirds of our patients. More data would be needed for other more difficult-to-treat infections, such as pneumonia, or for other microorganisms, such as *K. pneumoniae*. Moreover, our data extend to AMC and PTZ but not to other BLBLIs. In conclusion, our results suggest that AMC or PTZ, if used at adequate dosages, are suitable options for the definitive therapy of susceptible ESBL-EC strains causing BSI, mainly in the urinary and biliary tracts, which could help prevent overuse of carbapenems.

Notes

Acknowledgments. We thank the Spanish Group of the Study of Nosocomial Infections from the Spanish Society of Infectious Diseases and Clinical Microbiology for supporting the study.

Other participants from the ESBL-REIPI/GEIH group are Paloma Gijón (Hospital Universitario Gregorio Marañón, Madrid), José Ramón Hernández (Hospital Universitario Virgen Macarena, Sevilla), Jose M. Cisneros (Hospital Universitario Virgen del Rocío, Sevilla), Carmen Peña (Hospital Universitario de Bellvitge, Barcelona), Manuel Almela (Hospital Clinic, Barcelona), Benito Almirante (Hospital Universitario Vall d'Hebrón, Barcelona), Fabio Grill (Hospital Universitario Ramón y Cajal, Madrid; present address, Hospital Universitario La Paz, Madrid), Javier Colomina (Hospital de la Ribera, Alzira, Valencia), Monserrat Giménez (Hospital Germans Trias i Pujol, Badalona), Antonio Oliver (Hospital Son Espases, Palma de Mallorca), Juan Pablo Horcajada (Hospital Universitario Marqués de Valdecilla, Santander; present address, Hospital del Mar, Barcelona), Gemma Navarro (Corporacio Sanitaria Parc Taulí, Sabadell), and Ana Coloma (Hospital Santa Creu i San Pau, Barcelona).

Financial support. This study was funded by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, cofinanced by European Development Regional Fund "A way to achieve Europe" ERDF; Spanish Network for Research in Infectious Diseases (grant REIPI RD06/0008); Fondo de Investigación Sanitaria (grants 070190, 10/02021, and 10/01955); and Junta de Andalucía (grants 0063/2006, 0048/2008, and CTS-5259). The funders had no role in the design, analysis, writing of the manuscript, or decision to publish.

Potential conflicts of interest. J. R. B. has been a consultant for Wyeth, Merck, and Pfizer; has served as speaker for Wyeth, Merck, Pfizer, Astra-Zeneca, and GlaxoSmithKline; and has received research support from Merck and Wyeth. A.P. has been a consultant for Merck and Pfizer; has served as speaker for Wyeth, Astra-Zeneca, Merck, and Pfizer; and has received research support from Merck, Pfizer, and Wyeth. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Paterson DL, Bonomo R. Extended-spectrum β-lactamase: a clinical update. Clin Microbiol Rev **2005**; 18:657–86.
2. Pitout JDD, Laupland KB. Extended-spectrum β-lactamase–producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis **2008**; 8:159–66.
3. Rodríguez-Baño J, Pascual A. Clinical significance of extended-spectrum β-lactamases. Expert Rev Anti Infect Ther **2008**; 6:671–83.
4. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae. A potential threat. JAMA **2008**; 300:2911–3.
5. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis **2010**; 10:597–602.
6. Chen YH, Hsueh PR, Badal RE, et al. 2009 Asia-Pacific Smart Group. Antimicrobial susceptibility profiles of aerobic and facultative gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. J Infect **2011**; 62:280–91.
7. Hawser S, Hoban D, Bouchillon S, Badal R, Carmeli Y, Hawkey P. Antimicrobial susceptibility of intra-abdominal gram-negative bacilli from Europe: SMART Europe 2008. Eur J Clin Microbiol Infect Dis **2011**; 30:173–9.
8. Hoban DJ, Bouchillon SK, Hawser SP, Badal RE, Labombardi VJ, DiPersio J. Susceptibility of gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007–2008: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrob Agents Chemother **2010**; 54:3031–4.
9. Díaz MA, Hernández-Bello JR, Rodríguez-Baño J, et al. The diversity of *Escherichia coli* producing extended-spectrum ß-lactamases in Spain: second nationwide study. J Clin Microbiol **2010**; 48:2840–5.
10. Ruiz de Alegría C, Rodríguez-Baño J, Cano ME, et al. *Klebsiella pneumoniae* producing extended-spectrum β-lactamases in Spain: microbiological and clinical features. J Clin Microbiol **2011**; 49:1134–6.
11. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended spectrum beta-lactamase–producing Enterobacteriaceae: the role of piperacillin–tazobactam. Clin Microbiol Infect **2008**; 14:181–4.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet **2007**; 370:1453–7.
13. Rodríguez-Baño J, Navarro MD, Romero L, et al. Bacteremia due to extended-spectrum beta-lactamase–producing *Escherichia coli* in the CTX-M era: a new clinical challenge. Clin Infect Dis **2006**; 43:1407–14.
14. Rodríguez-Baño J, Alcalá JC, Cisneros JM, et al. Community infections caused by extended-spectrum β-lactamase–producing *Escherichia coli*. Arch Intern Med **2008**; 168:1897–902.
15. Doi Y, Paterson DL, Egea P, et al. Extended-spectrum and CMY-type β-lactamase–producing *Escherichia coli* in clinical samples and retail meat from Pittsburgh, US, and Seville, Spain. Clin Microbiol Infect **2010**; 16:33–8.
16. Rodríguez-Baño J, Picón E, Gijón P, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase–producing *Escherichia coli*: risk factors and prognosis. Clin Infect Dis **2010**; 50:40–8.
17. Rodríguez-Baño J, Picón E, Gijón P, et al. Risk factors and prognosis of nosocomial bloodstream infections caused by extended-spectrum β-lactamase–producing *Escherichia coli*. J Clin Microbiol **2010**; 48:1726–31.
18. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definition Conference. Crit Care Med **2003**; 31:1250–6.
19. Clinical and Laboratory Standards Institute 2010. Performance standards for antimicrobial susceptibility testing. In: 20th informational supplement. Approved standard M100-S20. Wayne, PA: Clinical and Laboratory Standards Institute, **2010**.
20. Clinical and Laboratory Standards Institute 2010. Performance standards for antimicrobial susceptibility testing. In: 20th informational supplement (June 2010 Update). Approved standard M100-S20-U. Wayne, PA: Clinical and Laboratory Standards Institute, **2010**.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. J Chron Dis **1987**; 40:373–83.

22. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med **1989**; 87:540–6.
23. Thomson KS, Moland ES. Cefepime, piperacillin-tazobactam, and the inoculum effect in tests with extended-spectrum beta-lactamase–producing Enterobacteriaceae. Antimicrob Agents Chemother **2001**; 45:3584–54.
24. López-Cerero L, Picón E, Morillo C, et al. Comparative assessment of inoculum effects on the antimicrobial activity of amoxicillin/clavulanate and piperacillin/tazobactam with ESBL-producing and non-producing *Escherichia coli* isolates. Clin Microbiol Infect **2010**; 16:132–6.
25. Rice LB, Carias LL, Shlaes DM. In vivo efficacies of beta-lactam-beta-lactamase inhibitor combinations against a TEM-26–producing strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother **1994**; 38:2663–4.
26. Thauvin-Eliopoulos C, Tripodi MF, Moellering RC Jr, Eliopoulos GM. Efficacies of piperacillin-tazobactam and cefepime in rats with experimental intra-abdominal abscesses due to an extended-spectrum beta-lactamase–producing strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother **1997**; 41:1053–7.
27. Mentec H, Vallois JM, Bure LA, Saleh-Mghir A, Jehl LF, Carbon C. Piperacillin, tazobactam, and gentamicin alone or combined in an endocarditis model of infection by a TEM-3–producing strain of *Klebsiella pneumoniae* or its susceptible variant. Antimicrob Agents Chemother **1992**; 36:1883–9.
28. Zimhony O, Chmelnitsky I, Bardenstein R, et al. Endocarditis caused by extended-spectrum-beta-lactamase–producing *Klebsiella pneumoniae*: emergence of resistance to ciprofloxacin and piperacillin-tazobactam during treatment despite initial susceptibility. Antimicrob Agents Chemother **2006**; 50:3179–82.
29. Coque TM, Novais A, Carattoli A, et al. Dissemination of clonally related *Escherichia coli* strains expressing extended-spectrum β-lactamase CTX-M-15. Emerg Infect Dis **2008**; 14:195–200.
30. Pitout JDD, Lea P, Church DL, Gregson DB, Laupland KB. Antimicrobial susceptibility of well-characterised multiresistant CTX-M–producing *Escherichia coli*: failure of automated systems to detect resistance to piperacillin/tazobactam. Int J Antimicrob Agents **2008**; 32:333–8.
31. Borer A, Gilad J, Menashe G, Peled N, Riesenberg K, Schlaeffer F. Extended-spectrum beta-lactamase–producing *Enterobacteriaceae* strains in community-acquired bacteremia in South Israel. Med Sci Monitor **2002**; 8:CR44–7.
32. Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum β-lactamases. Clin Infect Dis **2004**; 39:31–7.
33. Endimiani A, Luzzaro F, Brigante G, et al. *Proteus mirabilis* bloodstream infections: risk factors and treatment outcome related to the expression of extended-spectrum β-lactamases. Antimicrob Agents Chemother **2005**; 49:2598–605.
34. Tumbarello M, Sanguinetti M, Montouori E, et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum β-lactamase–producing *Enterobacteriaceae*: importance of inadequate initial antimicrobial treatment. Antimicrob Agents Chemother **2007**; 51:1987–94.
35. Apisarnthanarak A, Kiratisin P, Mundy LM. Predictors of mortality from community-onset bloodstream infections due to extended-spectrum β-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol **2008**; 29:671–4.
36. Gudiol C, Calatayud L, Garcia-Vidal C, et al. Bacteremia due to extended-spectrum β-lactamase–producing *Escherichia coli* (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother **2010**; 65:333–41.
37. Chaubey VP, Pitout JD, Dalton B, et al. Clinical outcome of empiric antimicrobial therapy of bacteremia due to extended-spectrum beta-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae*. BMC Res Notes **2010**; 3:116.
38. Lee CC, Lee NY, Yan JJ, et al. Bacteremia due to extended-spectrum-β-lactamase–producing *Enterobacter cloacae*: role of carbapenem therapy. Antimicrob Agents Chemother **2010**; 54:3551–6.
39. Qureshi ZA, Paterson DL, Paktis DL, et al. Risk factors and outcome of extended-spectrum beta-lactamase–producing *Enterobacter cloacae* bloodstream infections. Int J Antimicrob Agents **2001**; 37:26–32.
40. MacGowan A. Breakpoints for extended-spectrum beta-lactamase–producing Enterobacteriacae: pharmacokinetic/pharmacodynamic considerations. Clin Microbiol Infect **2008**; 14(Suppl 1):166–8.
41. Ambrose PG, Bhavnani SM, Jones RN. Pharmacokinetics-pharmacodynamics of cefepime and piperacillin-tazobactam against *Escherichia coli* and *Klebsiella pneumoniae* strains producing extended-spectrum beta-lactamases: report from the ARREST program. Antimicrob Agents Chemother **2003**; 47:1643–6.
42. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis **2007**; 44:357–63.