Clinical Infectious Diseases

MAJOR ARTICLE

Empiric Therapy With Carbapenem-Sparing Regimens for Bloodstream Infections due to Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae: Results From the INCREMENT Cohort

Zaira Raquel Palacios-Baena,[1] Belén Gutiérrez-Gutiérrez,[1] Esther Calbo,[2] Benito Almirante,[3] Pierluigi Viale,[4] Antonio Oliver,[5] Vicente Pintado,[6] Oriol Gasch,[7] Luis Martínez-Martínez,[8] Johann Pitout,[9] Murat Akova,[10] Carmen Peña,[11] José Molina Gil-Bermejo,[1] Alicia Hernández,[12] Mario Venditti,[13] Nuria Prim,[14] German Bou,[15] Evelina Tacconelli,[16] Mario Tumbarello,[17] Axel Hamprecht,[18] Helen Giamarellou,[19] Manel Almela,[20] Federico Pérez,[21] Mitchell J. Schwaber,[22] Joaquín Bermejo,[23] Warren Lowman,[24] Po-Ren Hsueh,[25] José Ramón Paño-Pardo,[26] Julián Torre-Cisneros,[27] Maria Souli,[28] Robert A. Bonomo,[29] Yehuda Carmeli,[22] David L. Paterson,[30] Álvaro Pascual,[1] and Jesús Rodríguez-Baño[1]; for the Spanish Network for Research in Infectious Diseases (REIPI)/European Study Group of Bloodstream Infections and Sepsis (ESGBIS)/INCREMENT Group[a]

[1]Unidad de Gestión Clínica de Enfermedades Infecciosas y Microbiología/Instituto de Biomedicina de Sevilla/Hospital Universitario Virgen Macarena/Universidad de Sevilla, and [2]Hospital Universitari Mútua de Terrassa, Universitat Internacional de Catalunya and [3]Hospital Vall d'Hebrón, Barcelona, Spain; [4]Teaching Hospital Policlinico S. Orsola Malpighi, Bologna, Italy; [5]Hospital Universitario Son Espases, Mallorca, [6]Hospital Ramón y Cajal, Madrid, [7]Hospital Parc Taulí, Barcelona, and [8]Hospital Universitario M. de Valdecilla-IDIVAL, Santander, Spain; [9]University of Calgary, Alberta, Canada; [10]Hacettepe University School of Medicine, Ankara, Turkey; [11]Hospital Bellvitge, Barcelona, and [12]Hospital Virgen de la Arrixaca, Murcia, Spain; [13]Policlinico Umberto I, Rome, Italy; [14]Hospital de la Santa Creu i Sant Pau, Barcelona, and [15]Complejo Hospitalario Universitario A Coruña, Spain; [16]Tübingen University Hospital and DZIF Partner Center, Germany; [17]Catholic University of the Sacred Heart, Rome, Italy; [18]Institut für Mikrobiologie, Immunologie und Hygiene, Universitätsklinikum Köln, Cologne, Germany; [19]Hygeia General Hospital, Athens, Greece; [20]Hospital Clinic, Barcelona, Spain; [21]Louis Stokes Cleveland Veteran Affairs Medical Center, Case Western Reserve University, Ohio; [22]Tel Aviv Sourasky Medical Center, National Center for Infection Control, Israel Ministry of Health, and Sackler Faculty of Medicine, Tel Aviv University; [23]Hospital Español, Rosario, Argentina; [24]Wits Donald Gordon Medical Centre, Johannesburg, South Africa; [25]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei; [26]Hospital La Paz, Madrid, and [27]Maimonides Biomedical Research Institute of Córdoba, Unidades de Gestión Clínica de Enfermedades Infecciosas y Microbiología, Reina Sofia University Hospital and University of Córdoba, Spain; [28]National and Kapodistrian University of Athens, School of Medicine, University General Hospital Attikon, Greece; [29]Research Service, Louis Stokes Cleveland Veterans Affairs Medical Center and Departments of Medicine, Pharmacology, Biochemistry, and Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Ohio; and [30]University of Queensland Centre for Clinical Research, Herston, Brisbane, Australia

Background. There is little information about the efficacy of active alternative drugs to carbapenems except β-lactam/β-lactamase inhibitors for the treatment of bloodstream infections (BSIs) due to extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-E). The objective of this study was to assess the outcomes of patients with BSI due to ESBL-E who received empiric therapy with such drugs (other active drugs [OADs]) or carbapenems.

Methods. A multinational retrospective cohort study of patients with BSI due to ESBL-E who received empiric treatment with OADs or carbapenems was performed. Cox regression including a propensity score for receiving OADs was performed to analyze 30-day all-cause mortality as main outcome. Clinical failure and length of stay were also analyzed.

Results. Overall, 335 patients were included; 249 received empiric carbapenems and 86 OADs. The most frequent OADs were aminoglycosides (43 patients) and fluoroquinolones (20 patients). Empiric therapy with OADs was not associated with mortality (hazard ratio [HR], 0.75; 95% confidence interval [CI], .38–1.48) in the Cox regression analysis. Propensity score–matched pairs, subgroups, and sensitivity analyses did not show different trends; specifically, the adjusted HR for aminoglycosides was 1.05 (95% CI, .51–2.16). OADs were neither associated with 14-day clinical failure (adjusted odds ratio, 0.62; 95% CI, .29–1.36) nor length of hospital stay.

Conclusions. We were unable to show that empiric treatment with OAD was associated with a worse outcome compared with carbapenems. This information allows more options to be considered for empiric therapy, at least for some patients, depending on local susceptibility patterns of ESBL-E.

Keywords. extended-spectrum β-lactamase–producing Enterobacteriaceae; bloodstream infections; therapy; antimicrobial resistance; aminoglycosides.

Extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-E) are now an important cause of bloodstream infections (BSIs) worldwide [1–3]. Carbapenems are generally considered the drugs of choice for serious infections due to ESBL-E [1] and are therefore increasingly being used for the empiric treatment of common infections. Consequently, their use has substantially increased, probably contributing to the spread of carbapenem resistance [4].

Received 30 March 2017; editorial decision 16 June 2017; accepted 13 July 2017; published online August 19, 2017.

[a]Members of the REIPI/ESGBIS/INCREMENT Group are listed in the Appendix.

Correspondence: J. Rodríguez-Baño, Unidad de Gestión Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Avda Dr. Fedriani, 3, Seville 41009, Spain (jesusrb@us.es).

Clinical Infectious Diseases® 2017;65(10):1615–23

DOI: 10.1093/cid/cix606

Any information about the efficacy of alternative empiric regimens for ESBL-E infections may help reduce the use of carbapenems. Recent data suggest that β-lactam/β-lactamase inhibitor combinations (BL/BLI) are good alternatives when used at appropriate doses, at least in many clinical situations [5–7]. However, there are few data on other antimicrobials; a recent meta-analysis showed higher mortality with empiric use of drugs other than BL/BLIs when compared to carbapenems [8]. However, many of the studies included did not stratify the data according to whether the isolates were susceptible or resistant, so that the negative impact on outcome could simply reflect the use of inactive drugs. Because a significant proportion of ESBL-E may be susceptible to alternative agents, any information about the potential efficacy of these alternative drugs would provide more options for empiric treatment when coverage of ESBL-E is needed.

The objective of this study was to assess the impact of empiric therapy with active drugs that were not carbapenems or BL/BLIs ("other active drugs" [OAD]), with a specific focus on aminoglycosides, on the outcomes of patients with BSI due to ESBL-E, and to compare these with carbapenems.

METHODS

We hypothesized that empiric treatment with OADs, including cephalosporins, aztreonam, aminoglycosides, fluoroquinolones, fosfomycin, tigecycline, and colistin, would be associated with higher mortality and lower cure rates compared with carbapenems. This hypothesis was constructed by merging others previously registered in the INCREMENT study (ClinicalTrials.gov identifier NCT01764490) that could not be investigated independently due to insufficient numbers of patients (Supplementary Table 1).

Study Design, Sites, and Participants

This study is part of the INCREMENT project, a multinational, retrospective cohort study of monomicrobial BSIs due to ESBL or carbapenemase-producing Enterobacteriaceae, diagnosed between 1 January 2004 and 31 December 2013. The methodology has been previously described in detail [7, 9, 10]. In summary, each center was asked to include up to 50 consecutive episodes of BSI due to ESBL-E, detected at each site by reviewing the microbiological records and bacteremia databases. The cases were included at 37 centers in 11 countries (Spain, Germany, Italy, Greece, Israel, Turkey, South Africa, Canada, United States, Argentina, and Taiwan). All patients were followed for 30 days after the day the blood cultures were taken (index date).

All patients with BSI caused by ESBL-E from the INCREMENT cohort who received initial therapy with an in vitro active carbapenem or OAD, either in monotherapy or in combination, were eligible for this analysis. Patients were included if the antibiotic was started <24 hours after the blood cultures were obtained. Patients who died within ≤24 hours after the blood cultures were obtained and subsequent episodes in the same patient were excluded.

The Institutional Review Board of the Hospital Universitario Virgen Macarena approved the study. Approval was also obtained at each participating center according to local requirements; the need for informed written consent was waived because of the observational nature of the study. This analysis was reported according to strengthening the reporting of observational studies in epidemiology (STROBE) recommendations [11] (Supplementary Table 2).

Variables and Definitions

The main outcome variable was 30-day all-cause mortality. Secondary outcomes were clinical failure at day 14 and length of hospital stay after BSI. Clinical failure was defined as death or a clinical situation similar to or worse than the first assessment or death due to any cause. The main exposure of interest was empiric antibiotic therapy with either an active carbapenem or OAD.

Other data collected included demographic variables; onset of infection (nosocomial [eg, presenting after 48 hours of admission] or community); chronic underlying conditions and severity according to the Charlson comorbidity index [12]; acute severity of baseline condition according to the Pitt score [13]; source of infection according to Centers for Disease Control and Prevention definitions [14]; presentation with severe sepsis or septic shock [15] on the index date; microorganism; and targeted antimicrobial therapy (administered once the susceptibility results were available). The previously published INCREMENT ESBL score for predicting 30-day mortality in patients with BSI due to ESBL-E, which included age, *Klebsiella* species, severity of underlying conditions, Pitt score, and presentation with severe sepsis or shock [10], was calculated for each patient.

Overall, antibiotic therapy was considered active if the isolate was susceptible or intermediate in vitro (see below); we included intermediate isolates as the outcome was mortality but performed a sensitivity analysis including only susceptible isolates. When only 1 active drug was administered, treatment was classified as monotherapy (regardless if other inactive drugs were administered); if >1 active drug was administered, it was considered to be combination therapy.

Standard phenotypic methods [16] were used at each participating center to test for ESBL production in isolates with diminished susceptibility to cephalosporins. The ESBL had been characterized in some isolates according to local objectives unrelated to those of this study, by polymerase chain reaction and DNA sequencing. Susceptibility was studied using automated systems or disk diffusion method and interpreted using 2010 Clinical and Laboratory Standards Institute (CLSI) breakpoints [16]. For isolates obtained before 2010, the category was reinterpreted according to minimum inhibitory concentration

(MIC) or inhibition zone diameters, using the 2010 CLSI criteria. When these were not available, the category provided by the local laboratory was used.

Statistical Analysis

Categorical variables were compared by the χ^2 test or Fisher exact test as appropriate, and continuous variables by the Mann-Whitney *U* test. The variable "center" was dichotomized as "high-mortality" or "low-mortality" hospital using TreeNet (Salford Systems, San Diego, California), controlling for all other variables. Univariate and multivariate analyses were performed using Cox proportional hazards regression and logistic regression analyses to identify associations between exposures and mortality until day 30 or clinical failure at day 14, respectively. A propensity score for receiving OAD was calculated as previously reported [7]; its predictive ability was estimated by calculating the area under the receiver operating characteristic curve (AUROC) with 95% confidence interval (CI). The propensity score was used as a covariate in multivariate analysis and for matching (see below). Variables with a *P* value ≤.2 in univariate analysis were included in the multivariate models and selected manually using backward stepwise regression. The variable "empiric treatment" (with OADs or carbapenem) was forced into the models. Interactions between empiric therapy and several covariates were explored. We calculated the variance inflation factor value for every variable included to check for collinearity. Sensitivity analyses for 30-day mortality were performed including changes in inclusion criteria and specific subgroups. A stratified analysis was also performed of patients with low (<11 points) and high (≥11 points) baseline mortality risk according to the INCREMENT ESBL score, as this cutoff appropriately defined patients with low and high risk of death [10]. Finally, patients treated with OADs and with carbapenems were matched (1:1) by the propensity score. Mortality in the matched pairs was compared by Cox regression. Statistical analysis was carried out using the SPSS software program (SPSS 21.0, IBM Corp, Armonk, New York).

RESULTS

Of 1004 patients with BSI due to ESBL-E included in the INCREMENT cohort, 357 received initial therapy with an active carbapenem or OAD and were eligible; 5 were excluded because antibiotics were started after 24 hours (none died) and 17 because they died in ≤24 hours (Figure 1). Therefore, 335 patients were included: 249 were treated empirically with a carbapenem and 86 with OADs. The ESBLs were characterized in 114 (34%) isolates; 92 of them (80.7%) produced CTX-M enzymes (CTX-M-1/15: 45 isolates; CTX-M-9/14: 27 isolates; CTX-M-2: 2 isolates; unspecified: 18 isolates).

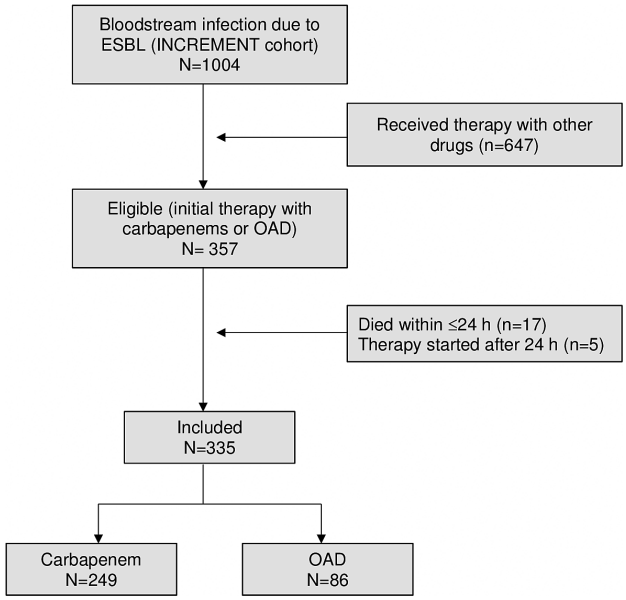

Figure 1. Flowchart of included patients. Abbreviation: ESBL, extended-spectrum β-lactamase; OAD, other active drug.

The features of patients and crude outcomes according to type of empiric therapy received are shown in Table 1. The drugs used for the OADs were aminoglycosides (43 patients; 2 with another active drug), fluoroquinolones (20 patients; 1 with another active drug), cephalosporins (7 patients), fosfomycin (5 patients; 1 with another active drug), colistin (5 patients; 2 with another active drug), trimethoprim-sulfamethoxazole (TMP-SMX) (4 patients), tigecycline (4 patients; 2 with another active drug), and aztreonam (2 patients). In the carbapenem group, 141 patients received meropenem, 61 imipenem, 46 ertapenem, and 1 doripenem; of these, 29 received another active drug. Overall, 43 (50%) of patients who received OADs as empiric therapy were changed to a carbapenem as definitive therapy.

Analysis of the Impact of Empiric Therapy on the 30-Day Mortality Rate

Mortality among patients treated with OADs or carbapenems were 18.6% (16/86) and 20.5% (51/249), respectively (absolute difference: −1.9%; 95% CI, −8.6 to 11.2). Kaplan-Meier curves for 30-day mortality did not show significant differences between patients treated empirically with carbapenems or OADs (log-rank test, *P* = .69) (Figure 2). Crude mortality rates according to the different antibiotics used as empiric therapy are shown in Table 2. Univariate and multivariate analyses of variables associated with 30-day mortality are shown in Table 3. Empiric therapy with the OADs rather than a carbapenem was not found to be associated with 30-day mortality (adjusted hazard ratio [HR], 0.75; 95% CI, .38–1.48; *P* = .42; Table 2); no significant collinearity between variables was shown. Interactions between empiric therapy and source, presentation with severe sepsis or shock, and microorganism showed no significant effects.

Table 1. Features of Patients and Outcomes According to Empiric Treatment

Variable	Carbapenems (n = 249)	Other Active Drugs (n = 86)	*P* Value
Male sex	153 (61.4)	41 (47.7)	.02
Age >50 y	191 (76.7)	70 (81.4)	.36
Nosocomial acquisition	128 (51.4)	53 (61.6)	.10
ICU admission	38 (15.3)	15 (17.4)	.63
Center with high mortality[a]	104 (41.8)	42 (48.8)	.25
Etiology			
Escherichia coli	164 (65.9)	55 (64)	.74
Klebsiella spp	75 (26.1)	22 (25.6)	.92
Other Enterobacteriaceae	20 (8)	9 (10.5)	.48
ESBL characterized	87 (34.9)	27 (31.3)	.21
Charlson index score ≥2	175 (70.3)	61 (70.9)	.9
Pitt bacteremia score >3	54 (21.7)	17 (19.8)	.7
Severe sepsis/septic shock	90 (36.1)	26 (30.2)	.32
Source			.06
Urinary tract	104 (41.8)	33 (38.4)	
Biliary tract	29 (11.6)	3 (3.5)	
Other intra-abdominal infection	27 (10.8)	9 (10.5)	
Respiratory tract	13 (5.2)	10 (11.6)	
Other	76 (30.6)	31 (36)	
Targeted treatment			<.001
Active carbapenem	238 (95.6)	43 (50)	
Active BL/BLI	2 (0.8)	4 (4.7)	
Other active drug	9 (3.6)	39 (45.3)	
Median INCREMENT ESBL score (IQR)	9 (6–12)	8 (5–12)	.76[b]
INCREMENT ESBL score ≥11	81 (32.5)	28 (32.6)	.99
Mortality at day 30	51 (20.5)	16 (18.6)	.70
Failure of treatment at day 14	53 (21.3)	14 (16.3)	.31
Median days of hospital stay after BSI (IQR)	14 (8–24)	14 (8–28)	.90[b]

Data are presented as No. (%) unless otherwise indicated. *P* values are calculated by χ^2 or Fisher test unless otherwise indicated.

Abbreviations: BL/BLI, β-lactam/β-lactamase inhibitor; BSI, bloodstream infection; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; IQR, interquartile range.

[a]Classified according to TreeNet (see Methods).

[b]Mann-Whitney *U* test.

The estimations of the associations of OADs with mortality in subgroups and in sensitivity analyses were consistent with the analysis in the whole cohort (Table 4).

A stratified analysis was also performed using Kaplan-Meier curves on the low-risk (<11 points) and high-risk (≥11) strata of the INCREMENT ESBL score; no significant differences of mortality were found for empiric treatment with carbapenems or with an OAD (*P* = .381 and .976, respectively, log-rank test; Figure 2). Finally, 60 pairs of patients treated with carbapenems and OADs were matched according to propensity score; the HR for 30-day mortality in the matched pairs was 0.68 (95% CI, .31–1.48; *P* = .33).

Analysis of the Impact of Empiric Therapy on the Rate of Clinical Failure at Day 14 and Length of Hospital Stay

The univariate and multivariate analyses of the association of OADs with clinical failure at day 14 are shown in Supplementary Table 3. Empiric treatment with OAD was not found to be significantly associated with failure (adjusted odds ratio, 0.62; 95% CI, .29–1.36; *P* = .24).

In patients discharged alive, the median length of stay was 16 days (interquartile range [IQR], 9–26) for patients treated empirically with carbapenems and 14 (IQR, 10–32) for patients treated with the OAD (*P* = .86); linear regression analysis after adjusting for propensity score did not show a significant association between empiric therapy with OAD and length of stay (*P* = .26).

Empiric Therapy of Bloodstream Infection due to Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae With Aminoglycosides

Of the 43 patients treated with aminoglycosides, 33 received another drug, which was active in 2 and inactive in 31 (18 a cephalosporin, 5 a fluoroquinolone, 5 a BL/BLI, and 3 others). The specific aminoglycosides used and dosing in 41 patients receiving aminoglycosides as the only active empiric drug are shown in Supplementary Table 4. The source of infection was the urinary tract in 14 (34.1%) patients, the biliary tract in 2 (4.9%), and other in 25 (61%). *Escherichia coli* was the causative microorganism in 28 (68.3%) patients; 16 (39%) presented with severe sepsis or shock. With respect to targeted treatment,

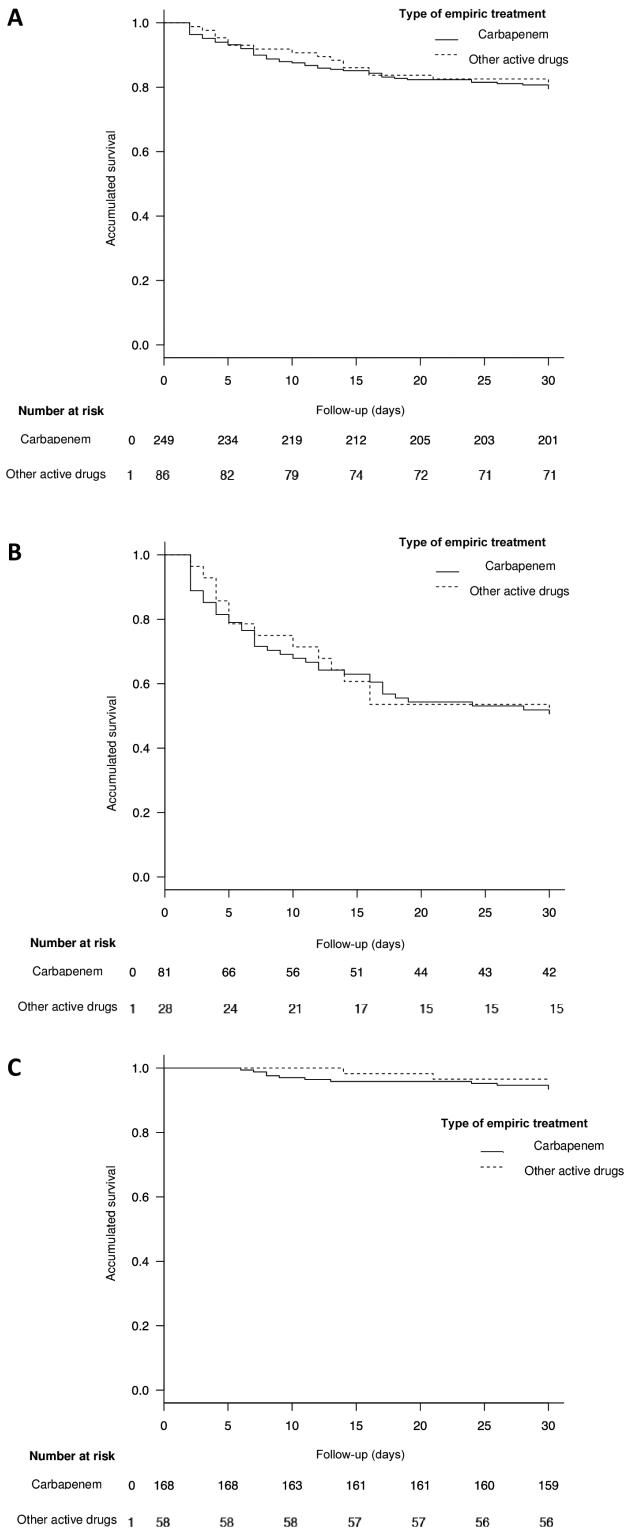

Figure 2. Kaplan-Meier curves for mortality according to empiric therapy. *A*, Whole cohort. *B*, Patients with a high INCREMENT extended-spectrum β-lactamase (ESBL) mortality score (≥11 points). *C*, Patients with a low INCREMENT ESBL mortality score (<11 points).

24 (58.5%) received a carbapenem, 2 (4.9%) a BL/BLI, and 15 (36.5%) another drug (13 continued with aminoglycosides, 1 cotrimoxazole, and 2 a cephalosporin). The median duration of treatment with aminoglycosides was 4 days (IQR, 2–6). Mortality among patients treated with aminoglycosides as the only active drug was 21.9% (9/41); the difference with carbapenems was 1.5% (95% CI, −9.8 to 16.9), and the adjusted HR for mortality was 1.05 (95% CI, .51–2.16; $P = .88$).

DISCUSSION

In this study, we were unable to demonstrate that empiric therapy with OAD among patients with BSIs due to ESBL-E was associated with worse outcomes in terms of mortality, clinical failure, or length of stay than carbapenems after controlling for confounders. Although these results cannot be interpreted as that carbapenems and OADs are equally effective because of the limited statistical power of the study, this is, to our knowledge, the biggest study providing comparative information about OADs, and we would have expected at least a trend favoring carbapenems if these drugs were clearly superior. While various drugs were used as OADs, the most common were aminoglycosides and fluoroquinolones, and the estimation of their individual effect in subgroup analyses was consistent with that of the whole OAD group. Importantly, in half of patients receiving OADs, a carbapenem was used as targeted therapy.

Because carbapenems are frequently considered the drugs of choice against ESBL-E and it is difficult to predict ESBL-E as the cause of an infection using epidemiological and clinical criteria [17], empiric use of these drugs has increased. Because de-escalation is used much less frequently than it should, finding alternatives to carbapenems in such situations would help reduce overuse of these drugs. The problem is that ESBL-E are frequently resistant to multiple drugs [1].

In the case of cephalosporins and aztreonam, the resistance is due to the ESBL itself. Their hydrolytic activity, however, is heterogeneous depending on the type of ESBL. As animal model data suggest that the activity of cephalosporins depends on the drug reaching enough time above the MIC regardless of ESBL production [18], the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and CLSI now recommend reporting susceptibility as tested irrespective of ESBL production. However, several studies showed higher mortality with cefepime for isolates with MICs ≤8 mg/L [19, 20]; in fact, CLSI lowered the susceptibility breakpoint to ≤2 mg/L, whereas it is ≤1 mg/L for EUCAST. In our study, only 9 patients were treated with cephalosporins or aztreonam, so no conclusions can be drawn for these antibiotics.

In the case of aminoglycosides or TMP-SMX, resistance in ESBL-E may be due to the presence of resistance genes located on the same plasmids containing the ESBL genes or on additional plasmids [1]. While plasmid-mediated genes can also partly affect the activity of fluoroquinolones, high-level resistance to them is usually due to quinolone-related chromosomal mutations [21]. There is nonetheless no obvious reason to think that any of these drugs would be less efficacious against ESBL-E

Table 2. Thirty-Day Mortality Associated With Empiric Treatment Received

Empiric Therapy	Deaths/Treated	High-Risk Score[a]	Low-Risk Score[a]
Carbapenem as only active drug	42/226 (18.6)	32/66 (48.5)	10/160 (6.2)
Carbapenem combined with other active drug	9/23 (39.1)	8/15 (53.3)	1/8 (12.5)
Cephalosporin as only active drug	2/7 (28.6)	1/2 (50)	1/5 (20)
Aminoglycoside as only active drug[b]	9/41 (21.9)	8/16 (50)	1/25 (4)
Fluoroquinolone as only active drug	2/19 (10.5)	2/2 (100)	0/17 (0)
Trimethoprim-sulfamethoxazole as only active drug	0/4 (0)	0/1 (0)	0/3 (0)
Tigecycline as only active drug	1/2 (50)	1/2 (50)	0
Others used as only active drug[c]	2/10 (20)	2/4 (50)	0/6 (0)
Other combinations[d]	0/4 (0)	0/1 (0)	0/3 (0)

Data are presented as No. (%).

[a]High (≥11 points) and low (<11 points) risk according to INCREMENT extended-spectrum β-lactamase score.

[b]Amikacin (28 patients), gentamicin (12), and tobramycin (1).

[c]Aztreonam (2), fosfomycin (5), and colistin (3)

[d]Other combinations of >1 active drugs were: tigecycline + colistin (2), fosfomycin + amikacin (1), levofloxacin + amikacin (1).

than against non-ESBL producers if they are susceptible. This is important because, while resistance to fluoroquinolones or TMP-SMX is very frequent in ESBL-E, a high proportion of isolates are susceptible to some aminoglycosides, although with major regional variations. For instance, amikacin is active against close to or >90% of ESBL-producing *E. coli* in the United States [22] or South Korea [23], and against ESBL-producing *K. pneumoniae* in Spain [24].

In a meta-analysis of randomized trials [25], aminoglycosides were shown to be as effective as the comparators in urinary tract infections. However, because renal toxicity is also more common with these drugs, they have been used less in clinical

Table 3. Univariate and Multivariate Analyses of Risk Factors Associated With All-Cause 30-Day Mortality Using Cox Regression

	Crude Analysis		Adjusted Analysis[a]	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Male sex	0.89 (.55–1.45)	.66		
Age >50 y	3.8 (1.52–9.45)	.004	4.25 (1.69–10.76)	.002
Nosocomial acquisition	2.13 (1.26–3.60)	.004		
Source				
Urinary or biliary tract	Reference		Reference	
Unknown	3.72 (1.87–7.38)	<.001	3.14 (1.53–6.43)	.002
Other	4.07 (2.21–7.48)	<.001	2.91 (1.54–5.52)	.001
ICU admission	3 (1.80–5.01)	<.001		
Microorganism				
Escherichia coli	0.36 (.22–.58)	<.001		
Klebsiella spp	2.63 (1.62–4.26)	<.001		
Other Enterobacteriaceae	1.43 (.68–2.99)	.34		
Charlson index score ≥2	4 (1.83–8.77)	.001	2.91 (1.31–6.45)	.008
Pitt bacteremia score >3	6.28 (3.87–10.19)	<.001	3.24 (1.94–6.03)	<.001
Severe sepsis/septic shock	5.43 (3.21–9.17)	<.001	2.40 (1.28–4.49)	.006
Empiric therapy				
Carbapenem	Reference		Reference	
Other active drugs	0.89 (.50–1.56)	.69	0.75 (.38–1.48)[b]	.42
Targeted therapy				
Carbapenem	Reference			
BL/BLI	0.76 (.1–5.48)	.78		
Other active	0.72 (.33–1.58)	.42		

The propensity score is included in the adjusted analysis. Variables included in the propensity score: hospital, age, sex, nosocomial or community-acquired infection, source of the infection, Charlson score, Pitt bacteremia score, and severity of presentation of symptoms (sepsis, severe sepsis, or shock). The area under the receiver operating characteristic curve of the propensity score for receiving other active drugs was 0.82 (95% CI, .77–.87).

Abbreviations: BL/BLI, β-lactam/β-lactamase inhibitor; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

[a]Center and propensity score are included.

[b]HR when propensity score was not included: 0.92 (95% CI, .52–1.65), $P = .79$.

Table 4. Subgroup and Sensitivity Analyses for the Impact of Empiric Therapy With Other Active Drugs Versus Carbapenems

Subgroup	Dead/Treated With Carbapenems	Dead/Treated With OAD	Adjusted HR (95% CI)	*P* Value
Male sex	29/153 (19)	8/41 (19.5)	1.13 (.5–2.55)	.75
Female sex	22/96 (22.9)	8/45 (18)	0.67 (.28–1.58)	.36
Severe sepsis/septic shock	37/90 (41.1)	10/26 (38.5)	1.05 (.51–2.15)	.87
Urinary tract infection	8/104 (7.7)	2/33 (6.1)	0.74 (.53–3.64)	.71
Non–urinary tract infection	43/145 (29.7)	14/53 (26.4)	0.93 (.49–1.77)	.84
Escherichia coli infection	23/164 (14)	6/55 (11)	0.61 (.23–1.58)	.31
Klebsiella spp infection	22/65 (33.8)	8/22 (36.4)	1.52 (.62–3.72)	.35
Only aminoglycosides as OAD	51/249 (20.5)	9/41 (21.9)	1.05 (.51–2.16)	.88
Only fluoroquinolones as OAD	51/249 (20.5)	2/19 (10.5)	0.79 (.17–3.51)	.76
Drugs other than aminoglycosides or fluoroquinolones as OAD	51/249 (20.5)	5/26 (19.2)	0.76 (.29–1.95)	.56
Carbapenems and BL/BLI in the comparator group	86/494 (17.4)	16/86 (18.6)	1.08 (.60–1.95)	.78
Targeted treatment with carbapenem	29/146 (20)	6/24 (25)	0.82 (.38–1.76)	.61
Including patients who died within ≤24 h or therapy started >24 h	65/268 (24.3)	19/89 (21.3)	0.90 (.53–1.52)	.70
Patients with intermediate isolates excluded	51/249 (20.5)	14/73 (19.2)	0.89 (.48–1.63)	.72

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BL/BLI, β-lactam/β-lactamase inhibitor; CI, confidence interval; HR, hazard ratio; OAD, other active drug.

practice in the last 20 years. Now, in the era of antimicrobial resistance, their utility must be reassessed and one possibility could be to consider them as options for preventing overuse of broad-spectrum drugs. Published clinical experience of aminoglycosides for serious ESBL-E infections is limited to case series in urinary tract infection [26, 27]. The present study included 41 patients who received aminoglycosides as the only active empiric drug; we could not find significantly different outcomes compared with carbapenems. Importantly, median duration of therapy with aminoglycosides was only 4 days, as many patients were changed to a different drug as targeted therapy. We did not collect information about nephrotoxicity, but we hypothesize that it might have been infrequent or not very relevant as no evident impact in length of stay was shown; if so, it might be explained by the short duration of therapy with these drugs. What our data suggest is that aminoglycosides could be used empirically (alone or added to a standard regimen) instead of using a carbapenem according to local susceptibility of ESBL-E for patients at risk of ESBL-E, and treatment may be tailored later according to susceptibility data, thus avoiding toxicity. This would be particularly useful for urinary tract sepsis, because the etiology will be known in most cases and also because of the proven efficacy of these drugs in this type of infection.

Our study has several limitations. Because it is not a randomized trial, unmeasured confounding variables or residual confounding cannot be ruled out. Data on clinical failure may be less reliable in a retrospective study, which is why we also measured a hard outcome such as mortality. The fact that OADs were not associated with outcomes may be due to lack of statistical power as shown by the wide 95% CIs of adjusted HRs; therefore, we would be cautious in the interpretation of these results, particularly in high-risk patients, such as those in septic shock. The number of patients receiving some of the regimens in the OAD group was too small for specific analyses to be performed. In this patient population, the underlying situation of the patients and the early initiation of any active drug seem to explain most of the outcome variability, making it more difficult to find the impact of one antibiotic over others; therefore, the results would only apply to patients with a similar background, but reinforce the message that alternatives to carbapenems should be considered in many situations. Moreover, recent changes in the epidemiology of ESBL-E should be taken into account, as our study concentrated on the period of time between 2004 and 2013. Some strengths of the study are its multinational character, the strict criteria used to assign patients to each treatment group, and the use of advanced methods for controlling confounding.

In conclusion, early administration of OADs for BSI due to ESBL-E does not seem to compromise outcome in comparison with carbapenems, and might be an option for empiric regimens for many patients, depending on local susceptibility patterns. This may be particularly applied to the use of aminoglycosides in urinary tract sepsis potentially caused by ESBL-E and would justify the design of a randomized trial; however, until more data are available, we would still recommend considering carbapenems or BL-BLI for patients at risk of ESBL-E presenting with septic shock or with a non–urinary tract source of sepsis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank the European Study Group of Bloodstream Infections and Sepsis (ESGBIS) from the European Society of

Clinical Microbiology and Infectious Diseases (ESCMID) for endorsing the INCREMENT project. We thank Virginia Palomo for her contribution in reviewing the database and Alejandro González for his work with the online database programming.

Financial support. The study was funded by the Ministerio de Economía y Competitividad-Instituto de Salud Carlos III through the following grants: Acción Estratégica en Salud (PI10/02021 and PI14/01832), and Plan Nacional de I+D+i, Subdirección General de Redes y Centros de Investigación Cooperativa, Spanish Network for Research in Infectious Diseases (REIPI RD 12/0015/0010 and RD16/0016/0001), co-financed by the European Development Regional Fund "A way to achieve Europe," Operative Programme Intelligent Growth 2014–2020. B. G. G., J. R. B., A. P. H., and Y. C. also received funds from the Innovative Medicines Initiative, the European Union's Seventh Framework Programme (FP7/2007–2013), and in-kind contributions from European Federation of Pharmaceutical Industries and Associations companies (COMBACTE-CARE project, agreement 115620). R. A. B. was also supported in part by funds and/or facilities provided by the Cleveland Department of Veterans Affairs, the Veterans Affairs Merit Review Program and the Geriatric Research Education and Clinical Center VISN 10 (VISN 10 GRECC), and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH) under award numbers R01AI072219 and R01AI063517.

Potential conflicts of interest. J. R. B. has been scientific coordinator for research projects for AstraZeneca and InfectoPharm, and speaker at accredited educational courses for Merck. R. B. has received research grants from the NIH, Veteran Affairs, AstraZeneca, Merck, Melinta, and Steris. D. L. P. has received honoraria for advisory board participation from Merck, AstraZeneca, Cubist, Pfizer, and Novartis. Y. C. has received grants, honoraria, travel support, consulting fees, and other forms of financial support from Achaogen, Allecra Therapeutics, AstraZeneca, Basilea Pharmaceutica LTD, bioMérieux, Cepheid, DaVolterra, Durata Therapeutics, Intercell AG, Merck, PPD, Proteologics, Rempex Pharmaceuticals, Rib-X Pharmaceuticals, Syntezza Bioscience LTD, and Takeda Pharmaceutical Company. B. A. has been a scientific advisor for AstraZeneca, Merck, Pfizer, Novartis, Astellas, and Gilead, and a speaker for AstraZeneca, Merck, Pfizer, Astellas, Gilead, and Novartis. A. P. has been a speaker for Merck and B Braun; has been a scientific advisor for Merck; and has received unrestricted research grants from B Braun and AstraZeneca. 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 RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev **2005**; 18:657–86.
2. Rodríguez-Baño J, Pascual A. Clinical significance of extended-spectrum beta-lactamases. Expert Rev Anti Infect Ther **2008**; 6:671–83.
3. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis **2008**; 8:159–66.
4. Van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence **2016**; 11:1–10.
5. Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual Á; Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group. 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. Clin Infect Dis **2012**; 54:167–74.
6. Harris PN, Yin M, Jureen R, et al. Comparable outcomes for β-lactam/β-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused by cefotaxime-resistant *Escherichia coli* or *Klebsiella pneumoniae*. Antimicrob Resist Infect Control **2015**; 4:14.
7. Gutiérrez-Gutiérrez B, Pérez-Galera S, Salamanca E, et al. A multinational, preregistered cohort study of β-lactam/β-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother **2016**; 60:4159–69.
8. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis. J Antimicrob Chemother **2012**; 67:2793–803.
9. Gutiérrez-Gutiérrez B, Bonomo RA, Carmeli Y, et al; REIPI/ESGBIS/INCREMENT Group. Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study. J Antimicrob Chemother **2016**; 71:1672–80.
10. Palacios-Baena ZR, Gutiérrez-Gutiérrez B, De Cueto M, et al; REIPI/ESGBIS/INCREMENT Group. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother **2017**; 72:906–13.
11. 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. J Clin Epidemiol **2008**; 61:344–9.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
13. 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.
14. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control **2008**; 36:309–32.
15. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit CareMed **1992**; 20: 864–74.
16. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 20th informational supplement, M100-S20. Wayne, PA: CLSI, **2010**.
17. Kengkla K, Charoensuk N, Chaichana M, et al. Clinical risk scoring system for predicting extended-spectrum β-lactamase-producing *Escherichia coli* infection in hospitalized patients. J Hosp Infect **2016**; 93:49–56.
18. MacGowan A. Breakpoints for extended-spectrum beta-lactamase-producing Enterobacteriacae: pharmacokinetic/pharmacodynamic considerations. Clin Microbiol Infect **2008**; 14(suppl 1):166–8.
19. Wang R, Cosgrove SE, Tschudin-Sutter S, et al. Cefepime therapy for cefepime-susceptible extended-spectrum β-lactamase-producing Enterobacteriaceae bacteremia. Open Forum Infect Dis **2016**; 3:ofw132.
20. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis **2013**; 56:488–95.
21. Briales A, Rodríguez-Martínez JM, Velasco C, et al. Prevalence of plasmid-mediated quinolone resistance determinants qnr and aac(6')-Ib-cr in *Escherichia coli* and *Klebsiella pneumoniae* producing extended-spectrum β-lactamases in Spain. Int J Antimicrob Agents **2012**; 39:431–4.
22. Hawser SP, Badal RE, Bouchillon SK, et al. Susceptibility of gram-negative aerobic bacilli from intra-abdominal pathogens to antimicrobial agents collected in the United States during 2011. J Infect **2014**; 68:71–6.
23. Cha MK, Kang CI, Kim SH, et al; Korean Network for Study on Infectious Diseases (KONSID). In vitro activities of 21 antimicrobial agents alone and in combination with aminoglycosides or fluoroquinolones against extended-spectrum-β-lactamase-producing *Escherichia coli* isolates causing bacteremia. Antimicrob Agents Chemother **2015**; 59:5834–7.
24. Ruiz de Alegría C, Rodríguez-Baño J, Cano ME, et al. *Klebsiella pneumoniae* strains producing extended-spectrum beta-lactamases in Spain: microbiological and clinical features. J Clin Microbiol **2011**; 49:1134–6.
25. Vidal L, Gafter-Gvili A, Borok S, Fraser A, Leibovici L, Paul M. Efficacy and safety of aminoglycoside monotherapy: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother **2007**; 60:247–57.
26. Ipekci T, Seyman D, Berk H, Celik O. Clinical and bacteriological efficacy of amikacin in the treatment of lower urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. J Infect Chemother **2014**; 20:762–7.
27. Han SB, Lee SC, Lee SY, Jeong DC, Kang JH. Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. BMC Infect Dis **2015**; 15:414.

APPENDIX

Members of the REIPI/ESGBIS/INCREMENT Project Group. J. Gálvez (Hospital Universitario Virgen Macarena, Seville, Spain); M. Falcone, A. Russo (Policlinico Umberto I, Rome,

Italy); G. Daikos (Laikon General Hospital, Athens, Greece); E. M. Trecarichi and A. R. Losito (Catholic University of the Sacred Heart, Rome, Italy); J. Gómez (Hospital Universitario Virgen de la Arrixaca, Murcia, Spain); E. Iosifidis and E. Roilides (Hippokration Hospital of Thessaloniki, Thessaloniki, Greece); I. Karaiskos (Hygeia General hospital, Athens, Greece); Y. Doi (University of Pittsburgh, Pittsburgh, USA); F. F. Tuon (Hospital da Universidade Federal do Paraná, Paraná, Brazil); F. Navarro and B. Mirelis (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); JA. Martínez, C. de la Calle and L. Morata (Hospital Clinic, Barcelona, Spain); R. San Juan and M. Fernández-Ruiz (Hospital 12 de Octubre, Madrid, Spain); N. Larrosa and M. Puig (Hospital Universitario Vall d'Hebrón, Barcelona, Spain); J. Molina and V. González (Hospitales Universitarios Virgen del Rocío y Virgen Macarena, Seville, Spain); V. Rucci (Hospital Español, Rosario, Argentina); E. Ruiz de Gopegui and C. I. Marinescu (Hospital Universitario Son Espases, Palma de Mallorca, Spain); M. C. Fariñas, M. E. Cano and M. Gozalo (Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander, Spain); M. Mora-Rillo (Hospital Universitario La Paz-IDIPAZ, Madrid, Spain); S. Gómez-Zorrilla and F. Tubau (Hospital de Bellvitge, Barcelona, Spain); S. Pournaras, A. Tsakris and O. Zarkotou (National and Kapodistrian University of Athens, Athens, Greece); Ö. K. Azap (Baskent University, Ankara, Turkey); A. Antoniadou and G. Poulakou (National and Kapodistrian University of Athens, School of Medicine University General Hospital Attikon, Chaidari, Greece); D. Virmani (University of Calgary, Calgary, Canada); Á. Cano, I. Machuca (Hospital Universitario Reina Sofía-IMIBIC, Córdoba, Spain); Ö. Helvaci and A. O. Sahin (Hacettepe University, Ankara, Turkey); P. Ruiz-Garbajosa (Hospital Ramón y Cajal, Madrid, Spain); M. Bartoletti and M. Giannella (Teaching Hospital Policlinico S. Orsola Malpighi, Bologna, Italy); S. Peter (Tübingen University Hospital, Tübingen, Germany); C. Badia and M. Xercavins (Hospital Universitario Mútua de Terrassa, Terrassa, Spain); D. Fontanals and E. Jové (Hospital Parc Taulí, Sabadell, Spain).