Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study

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Objectives: Data about the efficacy of ertapenem for the treatment of bloodstream infections (BSI) due to ESBL-producing Enterobacteriaceae (ESBL-E) are limited. We compared the clinical efficacy of ertapenem and other carbapenems in monomicrobial BSI due to ESBL-E.

Methods: A multinational retrospective cohort study (INCREMENT project) was performed (ClinicalTrials.gov identifier: NCT01764490). Patients given monotherapy with ertapenem or other carbapenems were compared. Empirical and targeted therapies were analysed. Propensity scores were used to control for confounding; sensitivity analyses were performed in subgroups. The outcome variables were cure/improvement rate at day 14 and all-cause 30 day mortality.

Results: The empirical therapy cohort (ETC) and the targeted therapy cohort (TTC) included 195 and 509 patients, respectively. Cure/improvement rates were 90.6% with ertapenem and 75.5% with other carbapenems ($P=0.06$) in the ETC and 89.8% and 82.6% ($P=0.02$) in the TTC, respectively; 30 day mortality rates were 3.1% and 23.3% ($P=0.01$) in the ETC and 9.3% and 17.1% ($P=0.01$) in the TTC, respectively. Adjusted ORs (95% CI) for

cure/improvement with empirical and targeted ertapenem were 1.87 (0.24–20.08; P=0.58) and 1.04 (0.44–2.50; P=0.92), respectively. For the propensity-matched cohorts it was 1.18 (0.43–3.29; P=0.74). Regarding 30 day mortality, the adjusted HR (95% CI) for targeted ertapenem was 0.93 (0.43–2.03; P=0.86) and for the propensity-matched cohorts it was 1.05 (0.46–2.44; P=0.90). Sensitivity analyses were consistent except for patients with severe sepsis/septic shock, which showed a non-significant trend favouring other carbapenems.

Conclusions: Ertapenem appears as effective as other carbapenems for empirical and targeted therapy of BSI due to ESBL-E, but further studies are needed for patients with severe sepsis/septic shock.

Introduction

In recent years, the spread of ESBL, particularly CTX-M family enzymes, in Enterobacteriaceae has become a serious public health problem worldwide.[1–3] Because carbapenems are considered the drugs of choice for treatment of severe infections caused by ESBL-producing Enterobacteriaceae (ESBL-E),[1–4] clinicians are increasingly forced to consider these drugs in different clinical situations. This may be leading to an increase in the consumption of carbapenems,[5] which is particularly worrisome in a scenario where carbapenem resistance in Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* is rapidly increasing.[6,7]

In contrast to the other carbapenems, ertapenem has no appreciable activity against *P. aeruginosa* or *A. baumannii*. In fact, some available data suggest that ertapenem may either not modify or positively impact the rates of carbapenem resistance.[8,9] Ertapenem shows *in vitro* activity against ESBL-E,[10] although comparative data on clinical efficacy in severe infections are limited.[11–14] Doubts have in fact been raised about its efficacy against specific bacterial species or sources of infection and in severely ill patients, because of the limited concentrations reached by ertapenem at the standard dose of 1 g/day.[15–17]

The objective of this study was to evaluate whether ertapenem was as efficacious as any other carbapenem for the treatment of bloodstream infections (BSI) due to diverse ESBL-E from different sources and in different clinical situations.

Patients and methods

Study design and patients

The INCREMENT project is a retrospective international cohort study that included consecutive patients with clinically significant BSI due to ESBL- or carbapenemase-producing Enterobacteriaceae from January 2004 to December 2013. The overall objective of the INCREMENT project was to evaluate the efficacy of different antimicrobial drugs and regimens for the treatment of BSI. Thirty-seven tertiary hospitals from 12 countries participated. The participating centres were contacted because of their previous experience of identifying target microorganisms and collecting data from patients with BSI. This analysis was reported according to the STROBE recommendations[18] (Table S1, available as Supplementary data at *JAC* Online).

For this analysis, patients with clinically significant monomicrobial BSI due to ESBL-E who received monotherapy with ertapenem or another carbapenem (including imipenem, meropenem or doripenem) were eligible. All isolates were susceptible to carbapenems according to CLSI criteria.[19] For isolates obtained before 2012, MICs were reviewed and the susceptibility category was assigned accordingly. For 19 isolates, the MIC was not available or the available data were an MIC equal to or below the older susceptibility breakpoint; these were considered susceptible if so reported by the local laboratory. All time-dependent variables were measured with

regard to the day when the blood cultures were drawn (considered as day 0). Data from patients were collected from the charts for 30 days after the diagnosis of BSI; mortality registers were also consulted if needed, when available. We constructed two non-mutually exclusive cohorts in order to analyse the impact of empirical and targeted therapies.

The empirical therapy cohort (ETC) included patients: (i) who were treated with a carbapenem as monotherapy; (ii) for whom therapy was started within 24 h of blood cultures; and (iii) for whom the carbapenem was administered for ≥48 h, with the single exception of patients who died before 48 h, who were included if death occurred after one complete day of therapy (and were excluded otherwise). For the ETC analysis, targeted therapy was considered a potential confounder. The targeted therapy cohort (TTC) included patients: (i) who received monotherapy with a carbapenem once the susceptibility profile of the isolate was known (patients were assigned to this drug); (ii) for whom the carbapenem was started in ≤5 days or continued with if used empirically; and (iii) for whom the carbapenem was administered for ≥50% of the total duration of antibiotic therapy for the episode unless switched before because of failure [in this case, the patient was included and categorized as clinical failure (see below)]. For patients who died while on targeted therapy, only those who died after at least one complete day of therapy with the targeted regimen were included. In the TTC, empirical therapy was considered a potential confounder.

The INCREMENT project was registered (ClinicalTrials.gov identifier: NCT01764490). It was approved by the Spanish Agency of Medicines (AEMPS; code JRB-ANT-2012-01) and the Hospital Universitario Virgen Macarena Institutional Review Board (code 1921), which waived the need to obtain written informed consent due to the observational nature of the study. Approval was also gained at participating centres, according to local requirements.

Variables and definitions

The main outcome variables were clinical response rate at day 14 and all-cause 30 day mortality. Clinical response was classified as: cure (resolution of all signs and symptoms related to the infection with no further need for antibiotic therapy); improvement (partial control or resolution of signs and symptoms related to the infection or complete resolution but with continued antibiotic therapy); or failure (a clinical situation qualified as similar to or worse than the one at diagnosis of bacteraemia, switched to another drug because lack of improvement or death due to any cause). For the analysis, clinical response was dichotomized as cure/improvement versus failure. The secondary outcome was length of hospital stay after BSI.

Data collected included: age; gender; nosocomial or community-onset acquisition; type and severity of underlying conditions using the Charlson comorbidity index[20] and McCabe classification;[21] hospital service; source of BSI according to clinical and microbiological data; severity of disease at BSI presentation according to the Pitt bacteraemia score;[22] severity of systemic inflammatory response syndrome at BSI presentation;[23] antimicrobial therapy (empirical and targeted); clinical response; mortality; improvement; and length of stay after BSI.

Clinically significant BSI was defined as bacteraemia occurring in a patient with criteria for systemic inflammatory response.[23] Nosocomial

acquisition was defined as BSI with onset of symptoms of infection >48 h after hospital admission or within 48 h of hospital discharge. Otherwise, the case was considered to be community onset. Antimicrobials administered before susceptibility results became available (according to the date of the microbiology report) were considered empirical; they were considered targeted thereafter. Therapy with ertapenem or other carbapenems was considered as monotherapy if no other drug(s) with intrinsic activity against Gram-negative organisms (including penicillins, cephalosporins, monobactams, fluoroquinolones, aminoglycosides, trimethoprim/sulfamethoxazole, fosfomycin or colistin) were coadministered, irrespective of isolate susceptibility.

Enterobacteriaceae were identified using standard microbiological techniques at each participating centre. ESBL production was screened in all isolates with diminished susceptibility to cephalosporins and confirmed according to standard procedures. CLSI recommendations were used for susceptibility interpretation.[24] Selected isolates from each centre were characterized by PCR and DNA sequencing using established methods.

Statistical analysis

Separate analyses were performed for the two cohorts. Mortality rates of patients treated with ertapenem or other carbapenems were plotted using Kaplan–Meier curves and compared using the log-rank test. Multivariate analyses were performed using linear, logistic or Cox regression as appropriate. Variables with a P value <0.2 in the bivariate analysis were introduced into models. A propensity score (the probability of receiving therapy with a carbapenem other than ertapenem), calculated using a non-parsimonious multivariate logistic regression model in which the outcome variable was therapy with a carbapenem different from ertapenem, was introduced into the models. Interactions between therapy with ertapenem or other carbapenems and other variables were explored and included if they caused a significant modifying effect. Variables were selected using a backward stepwise process and propensity scores and centres were forced into the final models. The Akaike information criterion[25] was used to select the final logistic models. The models chosen were those that minimized Kullback–Leibler divergence between the model and the actual data.

In the TTC, an additional analysis restricted to patients who were matched on the basis of propensity score was performed. Each patient who received targeted treatment with ertapenem was matched with one who received treatment with another carbapenem using callipers of width equal to 0.2 of the standard deviation of the logit of the propensity score. This analysis could not be performed in the ETC because only 15 couples could be matched. The analyses were performed using R (version 3.0.1) and SPSS 15.0 software. Additionally, classification and regression trees (CART)[26] were performed in the TTC (CART software 7.0, Salford Systems).

Results

The INCREMENT database includes 1005 patients with BSI due to ESBL-E; 195 and 509 patients from 30 centres were included in the ETC and TTC groups, respectively (Figure 1). The genes coding for ESBL were characterized from isolates in 175 patients. The ESBLs produced were CTX-M type in 141 cases (80.6%). The specific enzymes were: 38 CTX-M-15, 25 CTX-M-1, 23 CTX-M-14, 19 CTX-M-9, 2 CTX-M-2, 1 CTX-M-27 and 34 non-specified enzymes from the CTX-M family (one isolate produced 2 CTX-M enzymes); SHV type in 16 cases (9.1%); and TEM type in 18 cases (10.3%).

ETC

The ETC included 195 patients: 32 received empirical therapy with ertapenem and 163 with another carbapenem (128 meropenem and 35 imipenem). No patient received empirical therapy with doripenem. The features of the patients are shown in Table 1. Urinary tract infections (UTI) and biliary tract sources and Escherichia coli were more frequent among patients treated with ertapenem, while ICU admission, nosocomial infections, cancer and severe sepsis/septic shock were less frequent. The most frequent dose regimens were: for imipenem, 500 mg every 6 h (40%); for meropenem, 1 g every 8 h (65%); and for ertapenem, 1 g per day (84%). Doses were typically adjusted for patients with renal insufficiency according to local product information.

Cure/improvement rates at day 14 were 29/32 for ertapenem (90.6%) and 123/163 for other carbapenems (75.5%) ($P = 0.06$; absolute difference, 15.1%, 95% CI: 1.9%–25.9%). For imipenem and meropenem, cure/improvement rates at day 14 were 80.0% (28/35 patients) and 74.2% (95/128 patients), respectively ($P = 0.65$). Variables associated with cure/improvement in the univariate analysis are shown in Table S2. In the final multivariate model, empirical therapy with ertapenem showed no significant association with cure/improvement at day 14 compared with
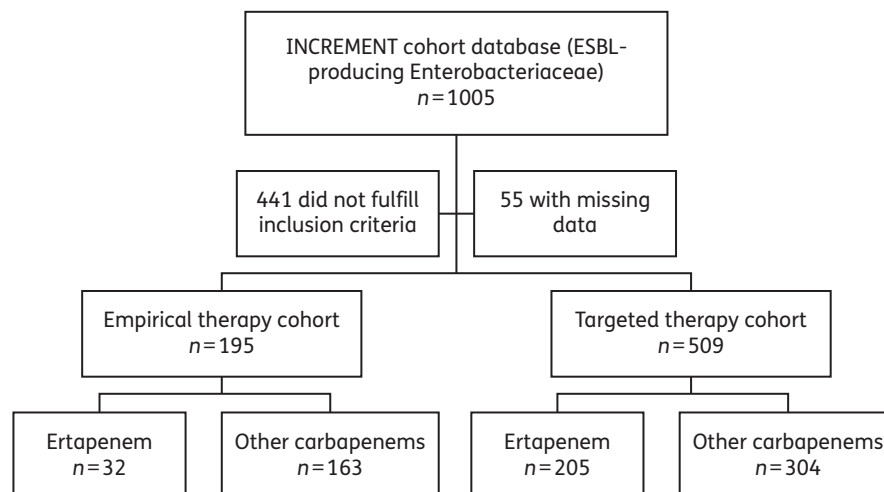

Figure 1. Patients selected.

Table 1. Characteristics of patients with bloodstream infections caused by ESBL-producing Enterobacteriaceae in the empirical therapy cohort[a]

	Empirical therapy cohort		
	ertapenem (n=32)	other carbapenems (n=163)	P value
Age, median (IQR)	66.5 (60.75–75.25)	66 (52–76)	0.43[b]
Male	20 (62.5)	97 (59.5)	0.75
Enterobacteriaceae			
E. coli	28 (87.5)	108 (66.3)	0.017
K. pneumoniae	3 (9.4)	44 (27.0)	0.033
others	1[c] (3.1)	11[d] (6.7)	0.44
Nosocomial acquisition	9 (28.1)	82 (50.3)	0.021
Source			
urinary tract	20 (62.5)	72 (44.2)	0.05
biliary tract	8 (25.0)	16 (9.8)	0.017
other	4[e] (12.5)	75[f] (46.0)	0.0003
ICU admission	1 (3.1)	26 (16.0)	0.05
Charlson index, median (IQR)	2 (1–3)	2 (2–4)	0.33[b]
McCabe score, non-fatal	19 (59.4)	76 (46.6)	0.19[b]
Pitt score, median (IQR)	0.5 (0–2)	2 (0–4)	0.30[b]
Severe sepsis/ septic shock	4 (12.5)	69 (42.3)	0.001
Cancer	4 (12.5)	65 (39.9)	0.003
Targeted therapy			
ertapenem	26 (81.3)	44 (27.0)	<0.0001
other carbapenem	2 (6.3)	97 (59.5)	<0.0001
other antimicrobial	4 (12.5)	22 (13.5)	0.88
Cure/improvement rate			
day 7	29 (90.6)	125 (76.7)	0.087
day 14	29 (90.6)	123 (75.5)	0.06
day 30	27 (84.4)	122 (74.8)	0.25
Mortality			
day 7	0 (0)	25 (15.3)	0.018
day 14	1 (3.1)	29 (17.8)	0.035
day 30	1 (3.1)	38 (23.3)	0.009
Hospital stay (days), median (IQR)	11 (8–14.5)	15 (9.2–23.8)	0.035[b]

[a]Except where otherwise specified, data represent numbers (%) of patients. P values were calculated by χ^2 test, except where otherwise specified.
[b]Mann–Whitney U-test.
[c]Proteus mirabilis, 1.
[d]Enterobacter cloacae, 11.
[e]Unknown, 2; intra-abdominal, 1; vascular, 1.
[f]Unknown, 24; vascular, 18; intra-abdominal, 15; pneumonia, 10; skin, 5; other, 2; osteoarticular, 1.

Table 2. Summary of crude and adjusted associations between therapy with ertapenem versus other carbapenems and outcomes

	OR	95% CI	P value
Cure/improvement			
empirical therapy cohort			
crude	2.94	0.97–12.7	0.09
adjusted (logistic regression)[a,b]	1.87	0.24–20.08	0.58
targeted therapy cohort			
crude	1.85	1.01–3.23	0.025
adjusted (logistic regression)[c,d]	1.04	0.44–2.50	0.92
targeted therapy propensity-matched cohorts			
crude	1.1	0.47–2.59	0.83
adjusted (conditional logistic regression)[e]	1.18	0.43–3.29	0.74

	HR	95% CI	P value
Mortality			
empirical therapy cohort			
crude	0.12	0.02–0.88	0.04
targeted therapy overall cohort			
crude	0.52	0.31–0.88	0.014
adjusted (Cox regression)[d,f]	0.93	0.43–2.03	0.86
targeted therapy propensity-matched cohorts			
crude	0.99	0.43–2.28	0.98
adjusted (Cox regression)[g]	1.05	0.46–2.44	0.90

[a]The complete model is shown in Table S2.
[b]The variables used to calculate the propensity score for receiving empirical therapy with a carbapenem different from ertapenem were: centre; age; gender; acquisition; type of hospital service; Pitt score; McCabe score; cancer; diabetes mellitus; chronic renal insufficiency; liver disease; cardiac disease; source; and presentation with severe sepsis/septic shock. The model showed a P value of 0.21 for the Hosmer–Lemeshow goodness-of-fit test and an area under the receiver operating characteristic curve of 0.96 (95% CI: 0.93–0.99).
[c]The complete model is shown in Table S3.
[d]The variables used to calculate the propensity score for receiving targeted therapy with a carbapenem different from ertapenem were: centre; age; gender; acquisition; type of hospital service; Pitt score; Charlson index; cancer; diabetes mellitus; chronic renal insufficiency; liver disease; cardiac disease; source; presentation with severe sepsis/septic shock; empirical therapy; and appropriate empirical therapy. The model showed a P value 0.84 for the Hosmer–Lemeshow goodness-of-fit test and an area under the receiver operating characteristic curve of 0.92.
[e]The complete model is shown in Table S7.
[f]The complete model is shown in Table S4.
[g]The complete model is shown in Table S8.

empirical therapy with other carbapenems (adjusted OR: 1.87; 95% CI: 0.24–20.08; P=0.58; Table S2 and Table 2). Controlling for the effect of centres, either individually or grouped, did not change the results.

The crude mortality rate of patients treated with ertapenem was 1/32 (3.1%) and 38/163 (23.3%) for those treated with another carbapenem, as shown in Table 1 and Figure S1(a) (P=0.012 by log-rank test and 0.009 by χ^2 test; absolute difference at day 30, −20.2%; 95% CI: −29.0% to −11.3%). Mortality rates

Table 3. Characteristics of patients with bloodstream infections caused by ESBL-producing Enterobacteriaceae in the targeted therapy cohort and the propensity-matched cohorts[a]

	Targeted therapy overall cohort			Targeted therapy propensity-matched cohorts		
	ertapenem (*n*=205)	other carbapenems (*n*=304)	*P* value	ertapenem (*n*=88)	other carbapenems (*n*=88)	*P* value
Age, median (IQR)	71 (60–81)	65 (52–77)	0.0001[b]	69 (57–77)	68 (55–78)	0.78
Male	119 (58.0)	176 (57.9)	0.97	64 (72.7)	51 (58.0)	0.04
Enterobacteriaceae						
E. coli	160 (78.0)	208 (68.4)	0.017	63 (71.6)	63 (71.6)	1
K. pneumoniae	34 (16.6)	67 (22)	0.13	19 (21.6)	18 (20.5)	0.85
others	11[c] (5.4)	29[d] (9.5)	0.086	6[e] (6.8)	7[f] (8.0)	0.77
Nosocomial acquisition	64 (31.2)	179 (58.9)	0.0001	41 (46.6)	40 (45.5)	0.88
Source						
urinary tract	121 (59.0)	112 (36.8)	0.0001	46 (52.3)	42 (47.7)	0.47
biliary tract	30 (14.6)	33 (10.9)	0.20	10 (11.4)	8 (9.1)	0.62
other	54[g] (26.3)	159[h] (52.3)	0.0001	32[i] (36.4)	38[j] (43.2)	0.35
ICU admission	13 (6.3)	51 (16.8)	0.0005	7 (8.0)	8 (9.1)	0.79
Charlson index, median (IQR)	2 (1–3)	2 (1–5)	0.0005[b]	2 (1–4)	2 (1–4)	0.77
McCabe score, non-fatal	133 (64.9)	133 (43.8)	0.0001[b]	45 (51.1)	51 (58.0)	0.36
Pitt score, median (IQR)	1 (0–2)	1 (0–3)	0.0003[b]	1 (0–2.25)	1 (0–2)	0.59[b]
Severe sepsis/septic shock	44 (21.5)	125 (41.1)	0.0001	28 (31.8)	27 (30.7)	0.87
Cancer	60 (29.3)	156 (51.3)	0.0001	32 (36.4)	27 (30.7)	0.42
Empirical therapy						
ertapenem	28 (13.7)	3 (1.0)	<0.0001	10 (11.4)	2 (2.3)	0.02
other carbapenem	32 (15.6)	78 (25.7)	<0.007	14 (15.9)	16 (18.2)	0.69
other active drug	68 (33.2)	95 (31.3)	0.65	27 (30.7)	30 (34.1)	0.63
Inactive/no drug	77 (37.6)	128 (42.1)	0.31	37 (42.0)	40 (45.5)	0.65
Active empirical therapy	128 (62.4)	176 (57.9)	0.53	51 (58.0)	48 (54.5)	0.62
Cure/improvement rate						
day 7	182 (88.8)	254 (83.6)	0.10	72 (81.8)	79 (89.8)	0.13
day 14	184 (89.8)	251 (82.6)	0.02	76 (86.4)	75 (85.2)	0.83
day 30	180 (87.8)	240 (78.9)	0.01	77 (87.5)	72 (81.8)	0.30
Mortality						
day 7	6 (2.9)	19 (6.3)	0.09	2 (2.3)	3 (3.4)	0.65
day 14	16 (7.8)	35 (11.5)	0.17	10 (11.4)	8 (9.1)	0.62
day 30	19 (9.3)	52 (17.1)	0.012	11 (12.5)	12 (13.6)	0.82
Hospital stay (days), median (IQR)	13 (8–19)	17 (12–28)	<0.0001[b]	12 (9–16)	18 (13–33.5)	<0.0001[b]

[a]Except where otherwise specified, data represent numbers (%) of patients. *P* values were calculated by χ^2 test, except where otherwise specified.
[b]Mann–Whitney *U*-test.
[c]*Enterobacter cloacae*, 8; *Proteus mirabilis*, 1; *Enterobacter aerogenes*, 1; *Klebsiella oxytoca*, 1.
[d]*Enterobacter cloacae*, 20; *Proteus mirabilis*, 1; *Enterobacter aerogenes*, 1; *Klebsiella oxytoca*, 3; *Citrobacter freundii*, 2; *Serratia marcescens*, 2.
[e]*Enterobacter cloacae*, 5; *Enterobacter aerogenes*, 1.
[f]*Enterobacter cloacae*, 5; *Proteus mirabilis*, 1; *Klebsiella oxytoca*, 1.
[g]Unknown, 18; intra-abdominal, 11; skin, 9; pneumonia, 6; vascular, 5; other, 3; osteoarticular, 2.
[h]Unknown, 55; intra-abdominal, 40; vascular, 28; pneumonia, 20; other, 8; skin, 6; osteoarticular, 1; nervous system, 1.
[i]Unknown, 10; intra-abdominal, 8; skin, 6; pneumonia, 3; vascular, 3; other, 1; osteoarticular, 1.
[j]Unknown, 9; intra-abdominal, 11; vascular, 8; skin, 4; pneumonia, 4; nervous system, 1; osteoarticular, 1.

were 24.2% (31/128 patients) with meropenem and 20.0% (7/35) with imipenem. Since only one patient died in the group of patients treated with ertapenem, univariate and multivariate Cox regression analysis of variables associated with mortality were not performed. Also, the small number of cases receiving ertapenem precluded the performance of a sensitivity analysis.

The median hospital stay after bacteraemia was significantly shorter for patients who received empirical therapy with ertapenem in comparison with other carbapenems (Table 1). The association was not significant after controlling for age, ICU, McCabe and propensity score in a regression linear model ($P=0.12$).

TTC

The TTC included 509 patients: 205 received targeted therapy with ertapenem and 304 other carbapenems (185 meropenem, 118 imipenem and 1 doripenem). The characteristics of the patients are shown in Table 3. UTI as source and *E. coli* were more frequent among patients treated with ertapenem, while ICU admission, nosocomial infections, cancer and severe sepsis/septic shock were less frequent. Patients treated with ertapenem were older and had lower Charlson and Pitt scores. There were no differences in ESBL type between the ertapenem and other carbapenem group (data not shown). The most frequent dose regimens were: for imipenem, 500 mg every 6 h (49.1%); for meropenem, 1 g every 8 h (50.8%); and for ertapenem, 1 g per day (84.3%). Doses were adjusted in patients with renal insufficiency, as noted previously.

Cure/improvement rates at day 14 were 184/205 (89.8%) and 251/304 (82.6%) for patients treated with ertapenem versus other carbapenems, respectively ($P=0.02$; absolute difference, 7.2%; 95% CI: 1.2%–13.14%). Cure/improvement rates were 81.1% (150/185 patients) and 84.7% (100/118) for patients treated with imipenem or meropenem, respectively. Univariate and multivariate analyses of variables associated with cure/improvement are shown in Table S3. In multivariate analysis, targeted therapy with ertapenem was not significantly associated with cure/improvement at day 14 compared with targeted therapy with other carbapenems (OR: 1.04; 95% CI: 0.44–2.50; $P=0.92$; Table 2 and Table S3). Interactions between carbapenem and source, severe sepsis/septic shock or aetiology were evaluated, although no significant modifying effects were found. The addition of individual or grouped centres did not change the results. Sensitivity analyses for cure/improvement at day 14 were performed. Adjusted ORs with 95% CI for subgroups of interest are shown in Figure 2; the results for subgroups were consistent for all subgroups, but a non-significant deviation in the CI for patients with severe sepsis/septic shock and those with an aetiology other than *E. coli* in comparison to other subgroups was noted.

Overall, mortality was lower among patients treated with ertapenem versus other carbapenems [$P=0.012$ by log-rank test, Figure S1(b); absolute difference for 30 day mortality, −7.8%; 95% CI: −13.6% to −2.0%]. Mortality rates were 17.3% (32/185 patients) for those treated with meropenem and 16.9% (20/118) with imipenem. Univariate and multivariate Cox regression analyses of variables associated with 30 day mortality are shown in Table 2 and Table S4. The adjusted HR (95% CI) for 30 day mortality of targeted therapy with ertapenem instead of other carbapenems in the final model was 0.93 (95% CI: 0.43–2.03; $P=0.86$). Interactions were not significant. Sensitivity analyses for mortality at day 30 were performed (Figure 3). Again, a non-significant deviation in the 95% CI for patients with severe sepsis/septic shock (Table S5) and those with an aetiology other than *E. coli* in comparison with other subgroups was noted.

To further test these relationships, a CART predictive model for 30 day mortality only for patients treated with ertapenem was performed, in order to identify mortality predictors. The final model obtained (Figure S2) showed that renal failure had a protective effect against mortality among patients with severe sepsis/septic shock treated with ertapenem. Mortality in patients with severe sepsis/septic shock treated with ertapenem was 0/7 and 9/32 (28.1%) in those with and without renal insufficiency, respectively. Curiously, three patients without renal insufficiency received >1 g/day and all three survived. The same analysis was performed only for patients treated with other carbapenems. In these patients, contrary to observations with ertapenem, renal failure increased the risk of death (41.9% versus 26.1%).

The median hospital stay after bacteraemia was significantly shorter for patients who received targeted therapy with ertapenem in comparison with other carbapenems (Table 3). The association remained after controlling for aetiology (bacteria), acquisition, Charlson, Pitt Score and propensity score in a regression linear model (average 9.6 days longer; 95% CI: 3.8–15.3; $P=0.001$).

Stratified analysis by quartiles of the propensity score in the TTC

We compared cure/improvement rates in patients treated with ertapenem and other carbapenems according to the quartile of
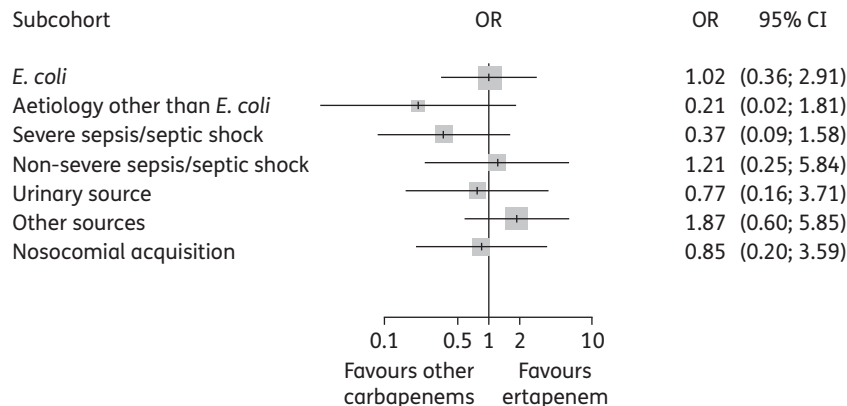

Subcohort	OR	OR	95% CI
E. coli		1.02	(0.36; 2.91)
Aetiology other than *E. coli*		0.21	(0.02; 1.81)
Severe sepsis/septic shock		0.37	(0.09; 1.58)
Non-severe sepsis/septic shock		1.21	(0.25; 5.84)
Urinary source		0.77	(0.16; 3.71)
Other sources		1.87	(0.60; 5.85)
Nosocomial acquisition		0.85	(0.20; 3.59)

Favours other carbapenems — Favours ertapenem

Figure 2. Sensitivity analyses for cure/improvement in the definitive therapy cohort.

Subcohort		HR	HR	95% CI
E. coli			0.49	(0.18; 1.31)
Aetiology other than *E. coli*			2.11	(0.39; 11.45)
Severe sepsis/septic shock			3.10	(0.86; 11.20)
Non-severe sepsis/septic shock			0.40	(0.10; 1.61)
Urinary source			0.91	(0.22; 3.79)
Other sources			0.99	(0.40; 2.48)
Nosocomial acquisition			0.50	(0.13; 1.96)

0.1   0.5   1   2   10

Favours   Favours other
ertapenem   carbapenems
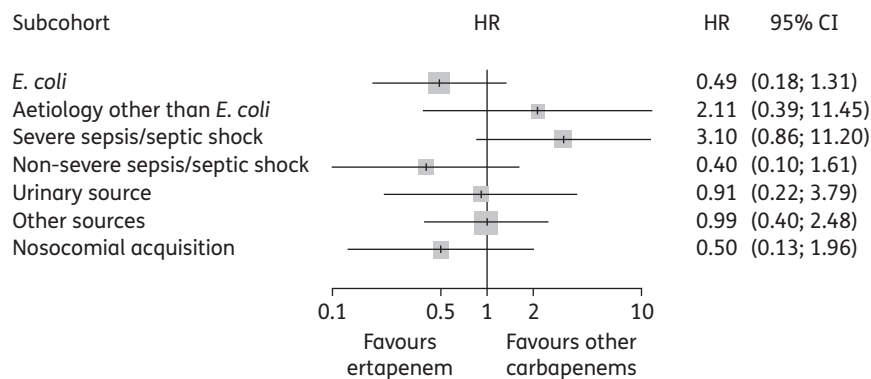
Figure 3. Sensitivity analyses for mortality in the definitive therapy cohort.
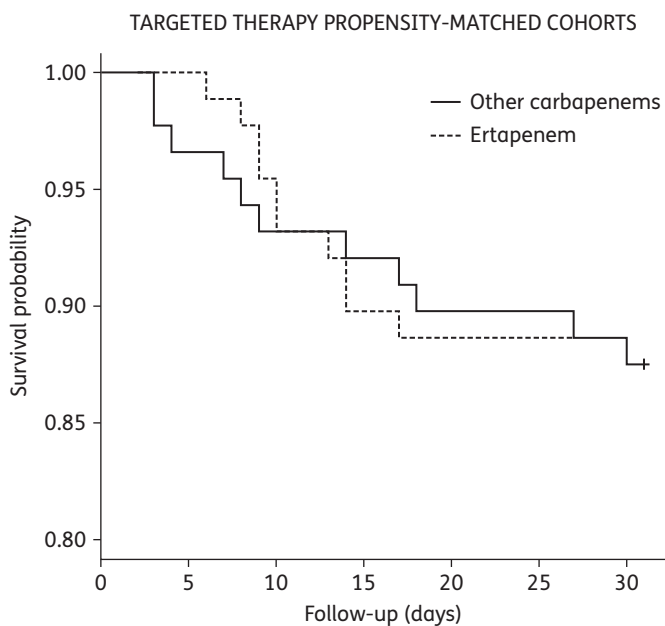
Figure 4. Kaplan–Meier curves for mortality in the targeted therapy propensity-matched cohorts of patients treated with ertapenem or other carbapenems.

the propensity score values (Table S6). Cure/improvement rates were similar in the second, third and fourth quartiles. However, only one patient was treated with ertapenem in the first quartile, meaning that no comparison could be made in patients with a very low probability of receiving ertapenem. In this quartile, 42.2% of patients had severe sepsis/septic shock, the bacterium was not *E. coli* in 37.5% and in 73.4% the source was not urinary. Mortality was similar for patients treated with ertapenem in the second, third and fourth quartiles and in none was it significantly higher than for patients treated with other carbapenems. In the first quartile, however, only one patient was treated with ertapenem, precluding any comparison (Table S6).

Propensity-matched TTCs

Using the propensity score, 88 pairs of patients receiving ertapenem or other carbapenems were matched. A comparison of the matched cohorts is shown in Table 3. Ertapenem was not associated with a worse rate of cure/improvement or mortality ($P=0.985$ by log-rank test, Figure 4) compared with other carbapenems, either in the crude comparison of matched cohorts or in multivariate analysis (Table 2 and Tables S7 and S8).

Discussion

Our results strongly support the hypothesis that active ertapenem is not inferior to other carbapenems for the treatment of BSI due to ESBL-E, although more data are needed for specific patient populations. Importantly, these data suggest that ertapenem, if active *in vitro*, may be used instead of the broader-spectrum carbapenems for the treatment of BSI due to any ESBL-E in many clinical situations.

To our knowledge, two previous studies have compared ertapenem and other carbapenems for the treatment of BSI due to ESBL-E and adjusted for confounders. Wu *et al.*[13] compared 17 patients who received definitive treatment with ertapenem and 22 who received imipenem or meropenem for ESBL-producing *E. coli* bacteraemia. Ertapenem was marginally associated with lower mortality in multivariate analysis; however, the results were not controlled for important confounders and probably suffered from collinearity with admission to ICU. In a retrospective, single-centre cohort study, Collins *et al.*[12] compared 24 and 103 patients receiving empirical therapy with ertapenem or other carbapenems, respectively, and 49 and 109 patients receiving the same antibiotics as targeted drugs for the treatment of BSI due to ESBL-producing *E. coli* or *Klebsiella pneumoniae*. No association between ertapenem therapy and mortality was found in multivariate analysis that included a propensity score.

In these studies, as in ours, ertapenem was more frequently used in lower-risk patients, including those with *E. coli* infections, a urinary source and without severe sepsis/septic shock. The bigger sample size in the present study provided us with an opportunity to examine the comparative efficacy of targeted therapy with ertapenem in these subgroups. While we found no differences according to source of BSI, adjusted estimates of outcomes in patients with non-*E. coli* Enterobacteriaceae or presenting with severe sepsis/septic shock tended somewhat towards favouring other carbapenems. It should be emphasized that we could not find ertapenem to be significantly associated with worse outcomes in any subgroups, but because of the lower statistical power in some of them, we do think that more studies are needed in these populations.

A possible explanation for a potential lower efficacy in septic-shock patients is the fact that critically ill patients frequently show lower concentrations of β-lactams due to the increased volume of distribution and/or clearance,[27] which may lead to insufficient pharmacokinetic target attainment (PTA) ($T_{>MIC}$) in the case of ertapenem, particularly in isolates with borderline susceptibility.[28] This would be less important with other carbapenems because of a higher margin for PTA. Although our data could not test this hypothesis, the fact that patients treated with ertapenem had a better prognosis in cases of renal insufficiency, which would increase exposure to ertapenem, is supportive. Whether higher doses of ertapenem (e.g. 1 g every 12 h) and/or serum level monitoring should be provided/performed in patients with septic shock, as has been suggested for burns patients,[29] would warrant specific studies.

Whether ESBL-E other than *E. coli* really have a worse outcome if treated with ertapenem could not be clarified with our data and requires further studies. Ertapenem MICs are usually higher for these isolates than for *E. coli*,[30] again suggesting that PTA may be compromised in some patients with those pathogens. However, we were unable to analyse the impact of MIC on outcome, because the MIC was not provided for all isolates (disc diffusion tests were used in some hospitals).

Mortality is frequently used as the only outcome variable in observational studies on therapy for BSI caused by antimicrobial-resistant pathogens. Although mortality is a 'hard' variable (not subject to opinion from investigators), it may not be sensitive enough to capture clinical failures of specific antibiotics because the patients may ultimately survive after changing therapy. This is why we also used clinical cure/improvement as an outcome variable, which is probably more sensitive although obviously 'soft' (potentially more prone to subjectivity). The definitions used are very similar to those used in randomized trials, but the investigators were not blinded and therefore the data on clinical response should be interpreted with caution. Nevertheless, the results are concordant with mortality.

Our study has other typical limitations of observational studies, including lack of randomization, the potential effects of unmeasured variables and residual confounding.[31] Also, by using strict criteria for inclusion, we increased internal validity, but may have reduced external validity. Finally, we cannot discard that some isolates were carbapenemase producers, as carbapenemases sometimes show low carbapenem MICs (e.g. in the susceptible range). However, this study also has some methodological strengths that should be taken into consideration: we used strict criteria for the assignment of patients to treatment arms; we also used several hard and soft outcome measures, including clinical response, mortality and length of hospital stay as outcome measures; advanced methods to control for confounding were used, such as the use of propensity scores (including propensity score matching) and sensitivity analysis;[31] only monomicrobial BSI were included; and, finally, the cases came from diverse geographical locations, and a large number of cases in the TTC were analysed, including patients with infections caused by non-*E. coli* species, non-urinary tract sources and severe sepsis/septic shock at presentation. However, a randomized controlled trial including severe patients would be the best way to demonstrate that ertapenem is not inferior to broader-spectrum carbapenems.

In conclusion, our data support the use of ertapenem in most cases of BSI due to ESBL-E whenever a carbapenem is to be used. More data are needed in patients with severe sepsis/septic shock or with non-*E. coli* infections.

Transparency declarations

J. R.-B. has been a speaker for Merck, Astellas, AstraZeneca, Pfizer and Novartis, has been scientific advisor for Merck, Achaogen, Roche, InfectoPharm and AstraZeneca, and has received unrestricted research grants from Novartis and Gilead. R. A. B. has received grants for research from NIH, Veteran Affairs, AstraZeneca, Merck, Melinta and Steris.

Supplementary data

Figures S1 and S2 and Tables S1 to S8 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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