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Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

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Objectives: To study the comparative mortality associated with carbapenems and alternative antibiotics for the treatment of patients with extended-spectrum β-lactamase (ESBL)-positive Enterobacteriaceae bacteraemia.

Methods: We searched systematically PubMed and Scopus databases for studies providing data for mortality among patients treated with carbapenems, β-lactam/β-lactamase inhibitor combinations (BL/BLIs) or non-BL/BLIs (mainly cephalosporins and fluoroquinolones), preferably as monotherapy. Studies focusing on patients of all ages with community- and healthcare-associated bacteraemia were eligible. Data were pooled using the technique of meta-analysis.

Results: Twenty-one articles, studying 1584 patients, were included. *Escherichia coli* and *Klebsiella pneumoniae* were the most commonly studied bacteria. Delay in appropriate treatment up to 6 days was reported. Carbapenems were used mainly as definitive therapy. Carbapenems were associated with lower mortality than non- BL/BLIs for definitive [risk ratio (RR) 0.65, 95% CI 0.47–0.91] and empirical (RR 0.50, 95% CI 0.33–0.77) treatment. No statistically significant differences in mortality were found between carbapenems and BL/BLIs administered as definitive (RR 0.52, 95% 0.23–1.13) or empirical (RR 0.91, 95% CI 0.66–1.25) treatment. BL/BLIs were not associated with lower mortality than non-BL/BLIs administered either definitively (RR 1.59, 95% 0.83–3.06) or empirically (RR 0.82, 95% 0.48–1.41). Data regarding subgroups according to the setting, comorbidity and bacterial species could not be extracted.

Conclusions: Based on data from non-randomized studies, carbapenems may be considered the treatment of choice for empirical treatment of patients with ESBL-producing Enterobacteriaceae bacteraemia. The role of BL/BLIs should be further evaluated for definitive treatment. Further research should focus on faster identification of ESBL-positive pathogens and potential differences in the treatment of each bacterial species.

Keywords: ESBLs, *Klebsiella*, *Escherichia*, *Proteus*, *Enterobacter*, mortality, Gram-negative

Introduction

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae have been increasingly implicated in healthcare-associated infections.[1–5] Carbapenems have been considered the treatment of choice.[1–5] However, the emergence of community-associated ESBL-positive infections[6,7] and increasing rates of carbapenem resistance in Enterobacteriaceae as well as other bacteria[8] necessitate a more judicious use of carbapenems. Cephalosporins have been associated with higher mortality even when the MIC for Enterobacteriaceae was within the susceptible range,[9,10] fluoroquinolone use is restricted by the frequently observed coexistence of ESBLs with mechanisms that mediate fluoroquinolone resistance[11] and data on effectiveness of empirical treatment with aminoglycosides, sulphonamides, tigecycline, colistin or fosfomycin are limited.[1,9,12]

β-Lactam/β-lactamase inhibitor combinations (BL/BLIs) have emerged as possible alternatives with the possible advantage of low association with development of infections caused by ESBL-producing bacteria.[13] A *post-hoc* analysis of six prospective studies suggested that there was no difference in mortality between carbapenems and BL/BLIs for the treatment of

ESBL-positive *Escherichia coli* bacteraemia.[14] We systematically reviewed the published evidence to study the comparative mortality associated with carbapenems and alternative antibiotics for the treatment of patients with ESBL-positive Enterobacteriaceae bacteraemia.

Methods

Literature search and study selection

Scopus and PubMed databases were searched until January 2012. The following search pattern was applied: (ESBL OR extended-spectrum β-lactamases) and (bacteraemia OR bloodstream infections). References of retrieved articles were hand searched. Articles published in languages other than English, Spanish, German, French, Italian or Greek were not eligible for inclusion.

Any published article reporting data on mortality of patients with bacteraemia due to ESBL-positive Enterobacteriaceae was considered eligible. Studies were included if they reported the mortality of patients receiving empirical or definitive treatment with any carbapenem in comparison with any other antibiotic, preferably administered as monotherapy. Patients of all ages with community-, hospital- and healthcare-associated bacteraemia were eligible for inclusion. Studies in which all patients received only carbapenems were excluded. Studies that included infections other than bacteraemia (primary, secondary or catheter related) were also excluded, as were case reports and abstracts from conferences.

Data extraction

Literature search, study selection and data extraction were performed independently by two investigators (G. S. T. and K. Z. V.). Any disagreement was resolved by consensus in meetings with all investigators. The extracted data included the characteristics of each study, its patient population, the studied pathogens, the testing method used for ESBL identification and its clinical outcomes. The corresponding authors were contacted via e-mail to provide outcome data according to the empirically or definitively prescribed antibiotics when such data were not available in the full article.

Definitions and outcomes

The outcome of this meta-analysis was the comparative all-cause mortality of patients receiving carbapenems or alternative antibiotics for bacteraemia due to ESBL-positive Enterobacteriaceae (and in the subsets of patients with bacteraemia due to *E. coli* and *Klebsiella pneumoniae*, if such data were available) as empirical or definitive treatment. The point at which mortality was recorded was the timepoint set in each study. Carbapenems were compared with BL/BLIs, non-BL/BLIs (all other antibiotics), fluoroquinolones, cephalosporins and all alternative antibiotics (BL/BLIs and non-BL/BLIs) in the primary analysis. In a secondary analysis, BL/BLIs were compared with non-BL/BLIs.

The definitions of nosocomial, healthcare-associated or community-onset bacteraemia were based on the definitions provided by each study. In general, bacteraemia was defined by the presence of at least one blood culture growing Enterobacteriaceae in addition to symptoms and signs compatible with bacteraemia and systemic inflammatory response syndrome (fever or hypothermia, systolic blood pressure <90 mmHg, tachycardia >90 beats/min and white blood cell count >11 000 cells/μL or <4000 cells/μL).

Empirical treatment was defined as prescription of antibiotics before culture results were available; empirical treatment was considered appropriate when the isolated pathogen was susceptible *in vitro* to the empirically administered antibiotic according to the CLSI breakpoints at the time of the study. Patients receiving empirical therapy with one class of antibiotics were included in the empirical treatment analysis regardless of the definitively administered regimen, unless they were excluded from the final analysis of the original study. Modification of treatment was defined as change to an effective antibiotic after the culture result was available according to the pathogen's susceptibility pattern. Definitive therapy was defined as appropriate empirical treatment plus correctly modified therapy.

Statistical analysis

Pooled risk ratios (RRs) and 95% CIs were calculated regarding all outcomes. Statistical heterogeneity between studies was assessed using a χ^2-test ($P<0.10$ was defined to indicate significant heterogeneity) and I^2 to denote the degree of heterogeneity (0%–40% no heterogeneity, 30%–60% moderate heterogeneity, 50%–90% substantial heterogeneity, 75%–100% considerable heterogeneity). The Mantel–Haenszel (M–H) fixed-effect model (FEM) was used when there was no significant statistical heterogeneity between the studies; otherwise, the DerSimonian–Laird random-effects model (REM) was used. Publication bias was assessed by the funnel plot method. The meta-analysis was performed with Review Manager for Windows, version 5.1. The Newcastle–Ottawa scale for assessment of risk of bias in non-randomized studies was used.

Results

Figure 1 shows the process for selection of the eligible studies. Forty-one articles did not report the required data and their corresponding authors were contacted. Three of them provided the requested data (one provided data for two articles);[15–18] data from one article could not be used because patients with and without bacteraemia were included.[15] Thus, of the retrieved articles, 21 were included in the meta-analysis.[14,16–35] One of the included studies was a *post-hoc* analysis of six prospective studies[14] in which the authors used only data regarding the comparative mortality of patients treated with carbapenems and BL/BLIs. However, two of these six studies also provided data regarding mortality of patients treated with non-BL/BLIs. These data were also used.[36,37]

Table 1 shows the characteristics of the included studies. The focus of the meta-analysis was similar to the scope of seven of the included studies.[14,19,23,30,31,33,35] Sixteen were retrospective[14,16–18,20,23–26,28–32,34,35] and five were prospective.[19,21,22,27,33] Sixteen studies were conducted after the year 2000,[14,16–23,26–28,30–32,34] two before 2000[24,33] and three enrolled patients from both periods.[25,29,35] Most were single-centre studies, and were performed in Asia,[16,19,21,24,28–32] Europe[14,23,25–27,35] or America;[17,18,22,34] one study was international[33] and one was conducted in South Africa.[20] Three studies were funded by pharmaceutical companies[18,22,34] and one by a pharmaceutical company and a physician association.[33] In-hospital mortality was reported in four studies,[19,22,24,25] 28 or 30 day mortality in 10 studies,[14,16–18,21,27–31,34] 21 day mortality in two studies[23,35] and 14 day mortality in four studies.[20,31–33] One study did not specify when mortality was assessed.[26]

Most of the enrolled patients had significant comorbidity that included solid organ or haematological malignancies, neutropenia, diabetes mellitus, chronic kidney or cardiovascular disease, prior hospitalization or antibiotic use. Community-associated, healthcare-associated and nosocomial episodes of

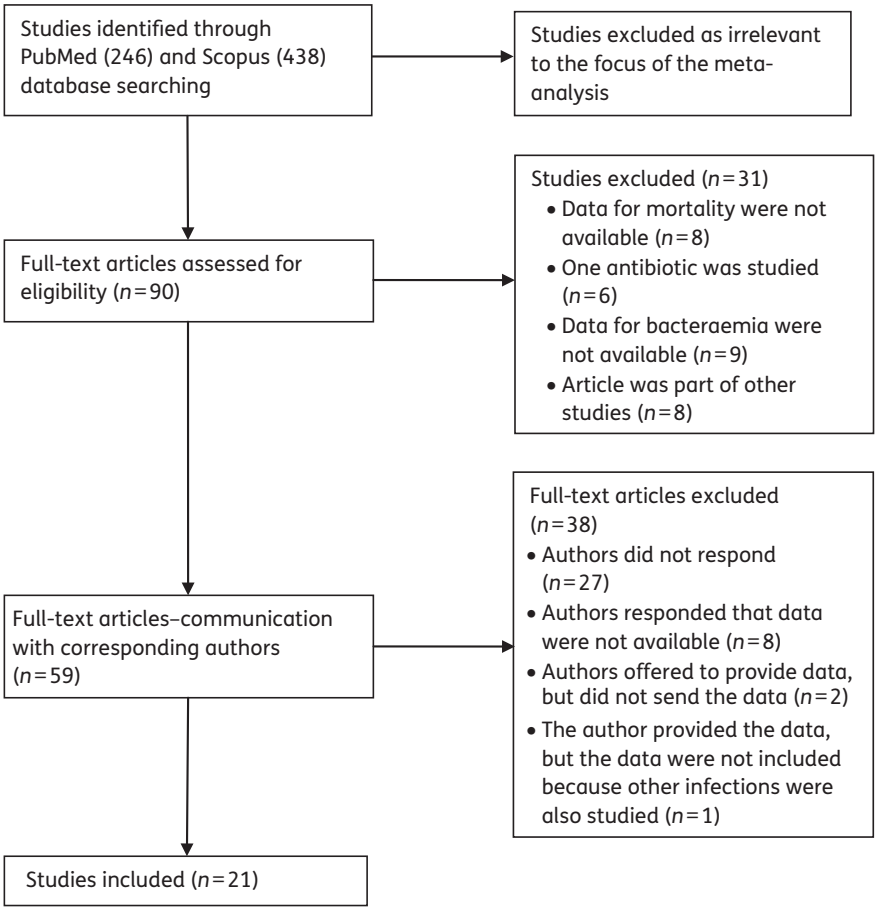

Figure 1. The process for selection of the eligible studies.

bacteraemia were studied together. *E. coli* and *K. pneumoniae* were the most frequently studied pathogens.

Predictors of mortality identified in the individual studies included severity of bacteraemia [as measured by Pitt bacteraemia score, septic shock, APACHE (acute physiological assessment and chronic health evaluation) II score, pneumonia or peritonitis, and intensive care unit (ICU) admission],[14,16,20,23,26–33,35] bacteraemia due to *K. pneumoniae*,[19] treatment with antibiotics other than carbapenems and/or BL/BLIs,[19,20,26,33] comorbidity[16,27–29,33] and inappropriate empirical treatment.[24,35] Appropriate empirical treatment ranged from 22% to 100%; 5 out of 13 studies that provided data reported that the proportion of patients receiving appropriate empirical treatment was lower than 50%;[16,18,19,26,27] 7 reported that 50%–70% of patients received appropriate empirical treatment.[17,21–23,25,32,35] In addition, a delay in the prescription of an appropriate regimen between 1 and 6 days was reported. Appropriate treatment was associated with lower mortality than inappropriate treatment (RR 0.64, 95% CI 0.46–0.88).

Table 2 shows the available data regarding mortality of 1584 patients with ESBL-positive bacteraemia included in the meta-analysis according to the definitively or empirically administered antibiotic. Table 3 summarizes the results of the meta-analysis. Publication bias was detected. Overall, carbapenems were more frequently used as definitive (∼35 patients per study reporting data) than as empirical (∼24 patients per study reporting data) antibiotic therapy. BL/BLIs were more frequently used as empirical (21 patients per study) than as definitive (11 patients per study) therapy. Besides BL/BLIs, cephalosporins, fluoroquinolones and aminoglycosides were used with decreasing frequency for the treatment of patients with ESBL-positive bacteraemia.

Data regarding mortality for patients treated definitively and empirically with carbapenems versus BL/BLIs were available from 11 and 13 studies, respectively. No difference in mortality was observed between carbapenems and BL/BLIs for both definitive (RR 0.52, 95% CI 0.23–1.13; Figure 2) and empirical (RR 0.91, 95% CI 0.66–1.25; Figure 3) treatment. Data regarding mortality of patients treated definitively and empirically with carbapenems and non-BL/BLI antibiotics were available from 13 and 11 studies, respectively. Mortality was lower with carbapenem than with non-BL/BLI antibiotic treatment for both definitive (RR 0.65, 95% CI 0.47–0.91; Figure 4) and empirical (RR 0.50, 95% CI 0.33–0.77; Figure 5) treatment. Carbapenems were not associated with lower mortality when they were compared with all studied antibiotics for empirical (RR 0.76, 95% CI 0.56–1.02) or definitive (RR 0.80, 95% CI 0.51–1.26) treatment. Carbapenems were associated with lower mortality than cephalosporins for both definitive (RR 0.34, 95% CI 0.22–0.52) and empirical (RR 0.51, 95% CI 0.32–0.82) treatment, and with lower mortality than fluoroquinolones for empirical (RR

Table 1. Characteristics of studies included in the meta-analysis

Author/year of publication (reference)	Study design, period, region	No. of patients, ESBL/total	Population characteristics, comorbidity	Bacteraemia characteristics	Bacteria	ESBL confirmation	Newcastle–Ottawa scale	Funding
Apisarnthanarak *et al.* (2008)[19]	SC case–control, 2003–07, Thailand	36/146	adults DM 42%, CVD 19%, CRD/F 17%	CO bacteraemia (primary 11%)	*E. coli* *K. pneumoniae*	disc diffusion	8	Thammasat University
Bin *et al.* (2006)[21]	SC prospective cohort, 2002–05, China	22/22	adults[a] malignancy 71%, neutropenia 14%	UD bacteraemia (primary 27%)	*E. coli*	disc diffusion	7	NAV
Chaubey *et al.* (2010)[22]	MC prospective cohort, 2000–07, Canada	79/79	adults[a] CRD/F 24%, malignancy 20%, DM 20%	HCA (nosocomial 30%) and CO (28%) bacteraemia (primary 49%)	*E. coli* *K. pneumoniae*	disc diffusion	6	Merck-Frosst Canada Inc.
Chung *et al.* (2012)[16]	SC retrospective cohort, 2005–10, Taiwan	122/122	adults CHF 49%, DM 30%, malignancy 28%, cirrhosis 28%, COPD 13%, CRD/F 9%	nosocomial (47%) and CO (53%) bacteraemia (primary 17%)	*E. coli*	disc diffusion	7	E-Da Hospital
De Rosa *et al.* (2011)[23]	SC retrospective cohort, 2000–07, Italy	77/128	adults surgery 27%, HM 11%, OLT 7%	HCA (nosocomial 56%) and CO (11%) bacteraemia (primary 47%)	*E. coli* *K. pneumoniae* *P. mirabilis*	Phoenix, MicroScan, Etest	7	University of Torino
Du *et al.* (2002)[24]	SC retrospective cohort, 1997–99, China	23/85	adults[a] malignancy 57%, CVD 26%, DM 17%	nosocomial bacteraemia (primary 39%)	*E. coli* *K. pneumoniae*	disc diffusion	7	NAV
Endimiani *et al.* (2005)[25]	SC retrospective cohort, 1997–2004, Italy	9/23	adults NAV	HCA (nosocomial 33%) bacteraemia (primary 56%)	*P. mirabilis*	PCR	6	Italian Ministry for Education
Ferrandez *et al.* (2011)[26]	retrospective cohort, 2000–06, Spain	53/53	adults malignancy 43%, DM 30%, CRD/F 21%, neutropenia 15%	nosocomial (65%), CO (35%) bacteraemia (primary 11%)	*E. coli* *K. pneumoniae*	disc diffusion, broth microdilution	7	NAV
Gudiol *et al.* (2010)[27]	SC prospective cohort, 2006–08, Spain	17/135	adults malignancy 100%, neutropenia 47%, DM 24%	HCA bacteraemia (primary 59%)	*E. coli*	disc diffusion	7	Spanish Ministry of Health
Kang *et al.* (2012)[29]	MC retrospective cohorts, 2008–10, S. Korea	114/114	NAV DM 25%, malignancy 23%,	UD bacteraemia (primary unknown)	*E. coli* *K. pneumoniae*	NAV	7	NAV
Kang *et al.* (2004)[28]	SC retrospective cohort, 1998–2002, S. Korea	133/133	adults[a] malignancy 50%, cirrhosis 17%	nosocomial (79%) and CO (21%) bacteraemia (primary 25%)	*E. coli* *K. pneumoniae*	disc diffusion	7	Korean Ministry of Health

Lee *et al*. (2010)[30]	SC retrospective cohort, 2001–08, Taiwan	121/206	adults DM 42%, malignancy 31%	nosocomial bacteraemia (primary 26%)	*Enterobacter cloacae*	Etest	7	Department of Health, Taiwan
Lee *et al*. (2006)[31]	SC retrospective cohort, 2004–05, Taiwan	27/27	adult ICU 48%, CRD/F 30%	UD bacteraemia (primary 0%)	*K. pneumoniae*	disc diffusion	7	none
Metan *et al*. (2009)[32]	MC retrospective cohort, 2003–07, Turkey	37/37	adults malignancy 78%, surgery 22%	nosocomial bacteraemia (primary 100%)	*E. coli*	disc diffusion	7	NAV
Paterson *et al*. (2004)[33]	post-hoc analysis of a MC prospective cohort, 1996–97, international	71/71	children and adults IMC 44%, ICU 39%	UD bacteraemia (primary 0%)	*K. pneumoniae*	broth dilution	8	Royal Australasian College of Physicians; Wyeth; Merck
Qureshi *et al*. (2011)[34]	MC retrospective cohort, 2005–08, USA	26/26	adults NAV	HCA (nosocomial 63%) and CO bacteraemia (primary 38%)	*Enterobacter cloacae*	PCR	6	AstraZeneca
Rodriguez-Bano *et al*. (2012)[14b]	post-hoc analysis of six prospective cohorts, 2001–07, Spain	192+48	adults NAV	nosocomial and CO bacteraemia (primary unknown)	*E. coli*	broth microdilution	7	Spanish Ministry of Science and Innovation
Tumbarello *et al*. (2007)[35]	SC retrospective cohort, 1999–2004, Italy	186/186	adults malignancy 52%, CRD/F 28%, DM 27%	HCA (90%) and CO bacteraemia (primary 46%)	*E. coli* *K. pneumoniae* *P. mirabilis*	disc diffusion	7	Italian Ministry for University and Scientific Research
Tuon *et al*. (2011)[18]	SC retrospective cohort, 2006–09, Brazil	63/104	adults mainly CVD 42%, malignancy 15%, DM 11%, CRD/F 10%	UD bacteraemia (primary unknown)	*K. pneumoniae*	NAV	6	Merck
Tuon *et al*. (2010)[17]	SC retrospective cohort, 2006–09, Brazil	28/58	adults mainly trauma 26%, CHF 21%, malignancy 18%, DM 14%	UD bacteraemia (primary unknown)	*Enterobacter* spp.	disc diffusion	5	none
Velaphi *et al*. (2009)[20]	SC retrospective cohort, 2002–03, South Africa	100	neonates NAV	HCA bacteraemia (primary unknown)	*K. pneumoniae*	NAV	6	NAV

CHF, chronic heart failure; CO, community onset; COPD, chronic obstructive pulmonary disease; CRD/F, chronic renal disease/failure; CVD, cardiovascular disease; DM, diabetes mellitus; HCA, healthcare associated; HM, haematological malignancies; IMC, immunocompromised; MC, multicentre; NAV, not available; OLT, orthotopic liver transplantation; SC single centre, UD, undefined location of bacteraemia acquisition.

[a]The data were not included in the methodology, but were suggested by the results.

[b]Data from this study are a summary of six prospective studies for carbapenems and BL/BLIs; data for the remaining antibiotics were available from two of these studies (references 36 and 37).

Table 2. Outcomes for mortality according to the antibiotics received

Author, year	Mortality, carbapenems, definitive	Mortality, carbapenems, empirical	Mortality, BL/BLIs, definitive	Mortality, BL/BLIs, empirical	Mortality, fluoroquinolones, definitive	Mortality, fluoroquinolones, empirical	Mortality, cephalosporins, definitive	Mortality, cephalosporins, empirical	Mortality, non-BL/BLIs, definitive	Mortality, non-BL/BLIs, empirical
Apisarnthanarak *et al*. (2008)[19]	NA	0/5 (0)	NA	1/10 (10)	NA	2/4 (50)	NA	10/17 (59)	NA	12/21 (57)
Bin *et al*. (2006)[21]	0/8 (0)	0/3 (0)	0/7 (0)	0/7 (0)	NA	0/2 (0)	0/7 (0)	0/10 (0)	0/7 (0)	0/12 (0)
Chaubey *et al*. (2010)[22]	4/30 (13)	0/10 (0)	6/28 (21)	6/16 (38)	1/4 (25)	3/13 (23)	NA	5/30 (17)	3/17 (18)	9/50 (18)
Chung *et al*. (2012)[16]	3/62 (5)	NA	0/3 (0)	NA	1/14 (7)	NA	1/15 (7)	NA	3/42 (7)	NA
De Rosa *et al*. (2011)[23]	NA	8/57 (14)	NA	2/8 (25)	NA	1/6 (17%)	NA	NA	NA	1/11 (9)
Du *et al*. (2002)[24]	1/13 (8)	NA	NA	NA	0/2 (0)	NA	2/7 (28)	NA	2/10 (20)	NA
Endimiani *et al*. (2005)[25]	0/2 (0)	NA	2/4 (50)	2/4 (50)	NA	NA	1/3 (33)	1/5 (20)	1/3 (33)	1/5 (20)
Ferrandez *et al*. (2011)[26]	16/30 (53)	2/6 (33)	0/5 (0)	6/13 (46)	1/4 (25)	5/11 (45)	1/2 (50)	9/10 (90)	3/9 (33)	12/22 (55)
Gudiol *et al*. (2010)[27]	NA	2/5 (40)	NA	3/6 (50)	NA	NA	NA	NA	NA	1/6 (17)
Kang *et al*. (2004)[28]	8/62 (13)	NA	NA	NA	3/29 (10)	NA	NA	NA	10/55 (18)	NA
Kang *et al*. (2012)[29]	NA	21/78 (27)	NA	8/36 (22)	NA	NA	NA	NA	NA	NA
Lee *et al*. (2010)[30]	5/53 (9)	4/24 (17)	3/3 (100)	1/13 (8)	3/16 (19)	1/3 (33)	9/38 (24)	11/56 (20)	13/58 (22)	13/77 (14)
Lee *et al*. (2006)[31]	5/20 (25)	NA	NA	NA	NA	NA	2/7 (29)	NA	2/7 (29)	NA
Metan *et al*. (2009)[32]	NA	7/22 (32)	NA	5/7 (71)	NA	NA	NA	4/7 (57)	NA	4/7 (57)
Paterson *et al*. (2004)[33]	1/27 (4)	NA	2/4 (50)	NA	4/11 (37)	NA	2/5 (40)	NA	13/29 (45)	NA
Qureshi *et al*. (2011)[34]	0/8 (0)	0/8 (0)	1/4 (25)	1/4 (25)	NA	NA	4/9 (44)	4/9 (44)	6/14 (43)	6/14 (43)
Rodriguez-Bano *et al*. (2012)[14a]	20/120 (17)	6/31 (19)	5/54 (9)	7/72 (10)	NA	4/11 (36)	NA	9/31 (29)	NA	14/48 (29)
Tumbarello *et al*. (2007)[35]	NA	1/28 (4)	NAV	4/33 (12)	NA	8/16 (50)	NA	NA	NA	13/36 (36)
Tuon *et al*. (2011)[18]	16/43 (37)	NA	1/2 (50)	NA	NA	NA	NA	NA	7/17 (41)	NA
Tuon *et al*. (2010)[17]	10/15 (67)	NA	4/4 (100)	NA	NA	NA	NA	NA	1/6 (17)	NA
Velaphi *et al*. (2009)[20]	NA	13/40 (32)	NA	12/48 (25)	NA	NA	NA	NA	NA	NA

NA, not available.

[a]Data from this study are a summary of six prospective studies for carbapenems and BL/BLIs; data for the remaining antibiotics were available from two of these studies (references 36 and 37).

Table 3. Summary of RR estimates on mortality of patients with ESBL-positive Enterobacteriaceae bacteraemia according to antibiotic comparisons

		Definitive treatment		Empirical treatment	
Antibiotic comparisons	No. of studies, D/E	no. of patients, *n*/*N* (%)	RR (95% CI), model used	no. of patients, *n*/*N* (%)	RR (95% CI), model used
Appropriate versus inappropriate	NA/11	NA	NA	89/406 (22) versus 141/370 (38)	**0.64 (0.44–0.88) REM (I^2 44%)**
Carbapenems versus BL/BLIs	11/13	75/398 (19) versus 24/118 (20)	0.52 (0.23–1.13) REM (I^2 71%)	64/317 (20) versus 56/273 (21)	0.91 (0.66–1.25) FEM (I^2 15%)
Carbapenems versus non-BL/BLIs	13/11	69/373 (18) versus 64/274 (23)	**0.65 (0.47–0.91) FEM (I^2 26%)**	30/199 (15) versus 85/304 (28)	**0.50 (0.33–0.77) FEM (I^2 13%)**
Carbapenems versus quinolones	7/8	38/300 (13) versus 13/80 (16)	0.63 (0.34–1.15) FEM (I^2 0%)	21/164 (13) versus 24/65 (37)	**0.34 (0.19–0.62) FEM (I^2 0%)**
Carbapenems versus cephalosporins	10/8	39/285 (14) versus 40/125 (32)	**0.34 (0.22–0.52) FEM (I^2 0%)**	19/100 (19) versus 52/170 (31)	**0.51 (0.32–0.82) FEM (I^2 0%)**
Carbapenems versus all	14/13	89/493 (18) versus 65/308 (21)	0.80 (0.51–1.26) REM (I^2 40%)	64/317 (20) versus 141/577 (24)	0.76 (0.56–1.02) FEM (I^2 18%)
BL/BLI versus non-BLBLIs	10/12	19/64 (30) versus 50/202 (25)	1.59 (0.83–3.06) REM (I^2 48%)	38/193 (20) versus 86/309 (28)	0.82 (0.48–1.41) REM (I^2 53%)

D, definitive treatment; E, empirical treatment; NA, not applicable.
Bold text indicates the outcomes with statistical significance.

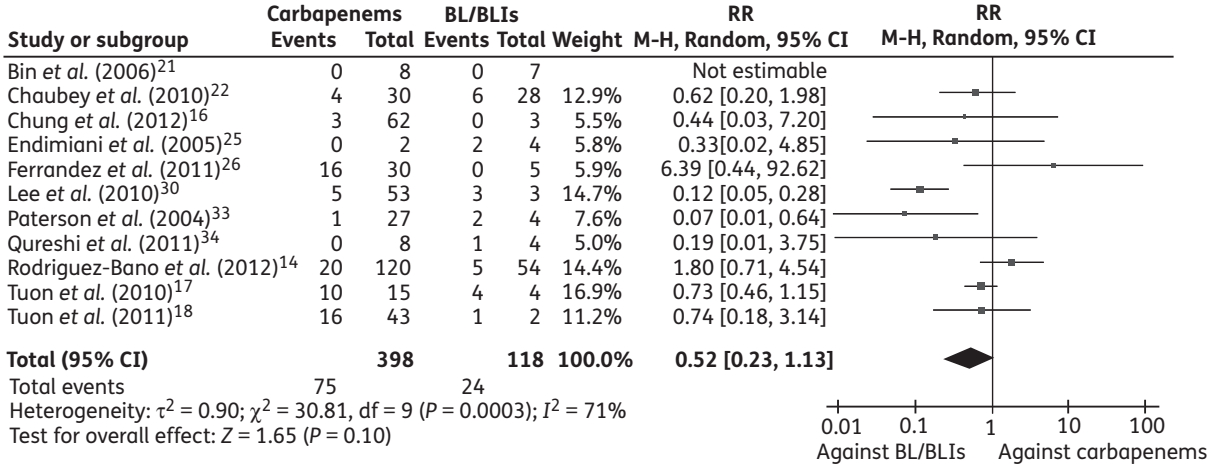

Figure 2. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated definitively with carbapenems versus BL/BLIs. Vertical line = 'no difference' point between the two regimens. Squares = RRs. Diamond = pooled RR for all studies. Horizontal lines = 95% CIs.

0.34, 0.19–0.62) though not definitive (RR 0.63, 95% CI 0.34–1.15) treatment. No difference in mortality was observed between BL/BLIs and non-BL/BLIs used either definitively (RR 1.59, 95% CI 0.83–3.06) or empirically (RR 0.82, 95% CI 0.48–1.41).

Data regarding the onset of bacteraemia (community, healthcare or nosocomial), its primary source (primary or secondary), ESBL identification method, Newcastle–Ottawa scale, study design, time of mortality assessment and specific bacterial species were limited and prohibited meaningful comparisons. Separate data for the outcome of patients who received a different empirical and definitive regimen were also not available. In addition, the data from the studies that evaluated mortality of patients infected specifically by *E. coli* or *K. pneumoniae* were too limited to allow for meaningful comparisons as the authors either studied a small number of patients or did not provide data for all antibiotic comparisons. Finally, the outcomes were not different between prospective and retrospective studies.

Discussion

Carbapenems were associated with lower mortality than non-BL/BLIs for both definitively and empirically treated patients with ESBL-positive bacteraemia. There was no difference in mortality when carbapenems were compared with BL/BLIs alone or with all alternative antibiotics. Carbapenems were used as definitive treatment

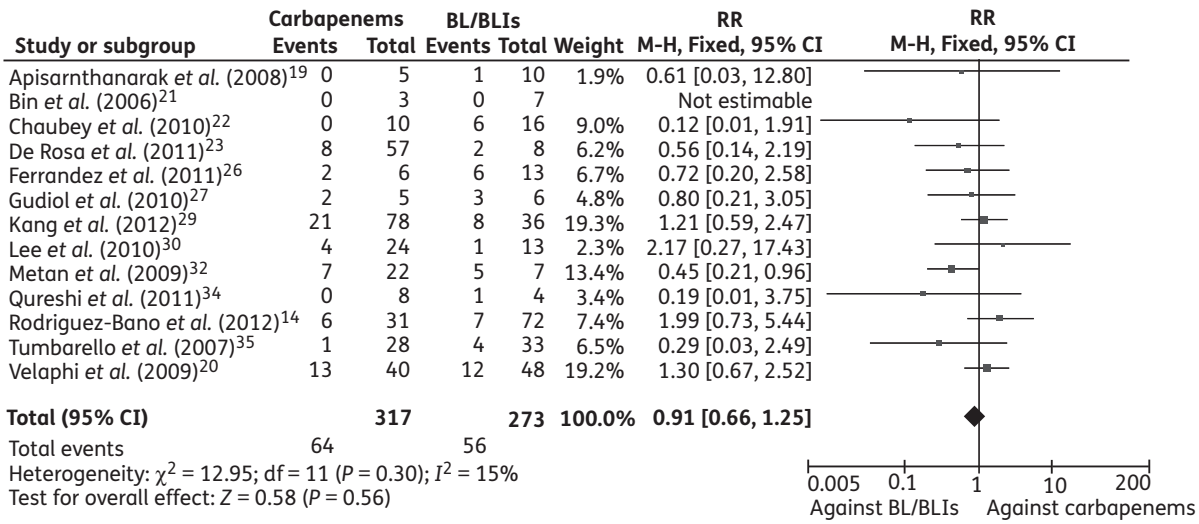

Figure 3. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated empirically with carbapenems versus BL/BLIs. Vertical line = 'no difference' point between the two regimens. Squares = RRs. Diamond = pooled RR for all studies. Horizontal lines = 95% CIs.

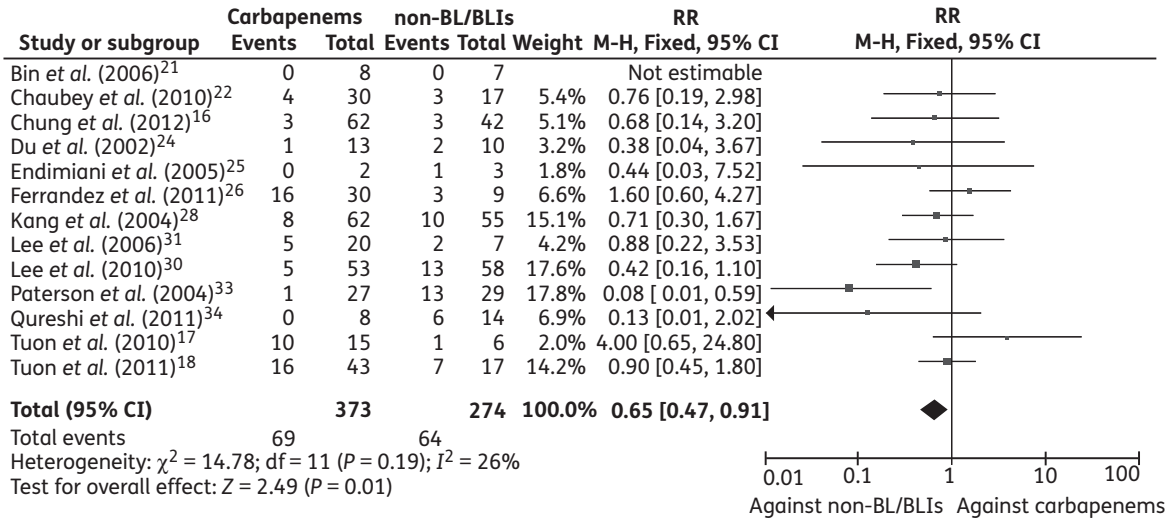

Figure 4. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated definitively with carbapenems versus non-BL/BLIs. Vertical line = 'no difference' point between the two regimens. Squares = RRs. Diamond = pooled RR for all studies. Horizontal lines = 95% CIs.

more frequently than as empirical treatment. Finally, BL/BLIs were not associated with lower mortality than non-BL/BLIs.

Although no statistical difference in mortality was shown between carbapenems and BL/BLIs, several issues need to be addressed. First, several of the patients who received empirical treatment with BL/BLIs finally received definitive therapy with carbapenems. As a result, we cannot conclude whether the observed mortality among patients on BL/BLIs should be attributed solely to these antibiotics. This clinical heterogeneity might explain the substantial statistical heterogeneity observed in the analysis of definitive treatment. Second, BL/BLIs can be inactivated by the presence of β-lactamases that do not belong to the ESBL group. There is also evidence that the MICs of piperacillin/tazobactam depend on the bacterial load; when the inoculum rises, so does the MIC. In addition, reduced activity of β-lactamase inhibitors has been documented due to porin loss in ESBL-positive strains.[5]

The resistance rate among ESBL-producing Enterobacteriaceae was higher to BL/BLIs than to carbapenems. The included studies reported that susceptibility of ESBL-producing Enterobacteriaceae to amoxicillin/clavulanate ranged from 4% to 100%, while susceptibility to piperacillin/tazobactam varied from 22% to 100%. *Proteus mirabilis* was the microorganism most susceptible to both antibiotics (~100% in all of the included studies). On the other hand, the susceptibility of *E. coli* varied between 4% and 67% for amoxicillin/clavulanate and between 22% and

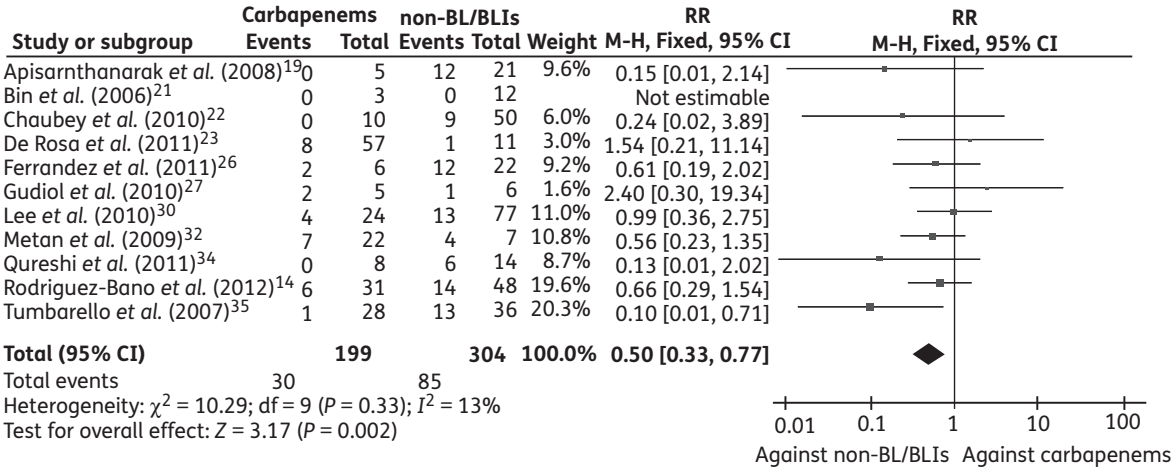

Figure 5. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated empirically with carbapenems versus non-BL/BLIs. Vertical line = 'no difference' point between the two regimens. Squares = RRs. Diamond = pooled RR for all studies. Horizontal lines = 95% CIs.

95% for piperacillin/tazobactam and the susceptibility of *K. pneumoniae* ranged from 54% to 64% for piperacillin/tazobactam. The susceptibility of the studied Enterobacteriaceae to carbapenems ranged from 95% to 100%.[16,23,26,32,35–37] In fact, only two studies reported that the susceptibility of *K. pneumoniae* strains to carbapenems was 95%, while in all others all isolates were susceptible to carbapenems. Other studies not included in the meta-analysis showed similar susceptibility trends,[38–41] suggesting that appropriate empirical treatment could be attained more often with prescription of carbapenems.

The choice of the empirical regimen depends on several parameters, including the history of the patient, the severity of bacteraemia, its primary site and the local patterns of susceptibility. It has been suggested that a non-urinary source of ESBL-positive bacteraemia is associated with higher mortality,[14,26] while an unidentified source of bacteraemia is associated with worse outcomes.[35] In addition, the outcome of infections depends on the implementation of additional therapeutic measures, including surgical procedures. Finally, physicians may select a broader-spectrum antibiotic or a combination of antibiotics for more severe infections. Since none of the studies included in the meta-analysis was a randomized controlled trial and data were not available for sensitivity analyses according to the aforementioned factors, their contribution to patient outcomes could not be estimated.

When interpreting the results of this meta-analysis we must also consider its limitations. First, most of the included studies were not designed to study the alternative options to carbapenems for ESBL-positive Enterobacteriaceae bacteraemia. Thus, data were not available to adjust for confounding factors. Second, several antibiotics of the same class had been used for both carbapenems and their comparators. In addition, although the majority of studies reported on appropriate empirical antibiotic treatment, they did not report outcomes on adequate treatment (plus correct dosing, sufficient duration of administration and so on).[42]

Third, although only studies on patients with ESBL-positive bacteraemia were included in the meta-analysis, their populations were heterogeneous since the source of bacteraemia varied significantly between studies. In addition, although *E. coli* and *K. pneumoniae* bacteraemias were predominantly studied, *Enterobacter* spp. and *P. mirabilis* bacteraemias were also included. It has been suggested that bacteraemia due to *K. pneumoniae* is associated with higher mortality than *E. coli* bacteraemia.[19] Unfortunately, the available data precluded a meaningful analysis according to specific species.

Fourth, patients with community-associated, healthcare-associated and nosocomial bacteraemia were included. It is possible that variables that might influence mortality can be found less commonly in patients in the first group.

Fifth, several of the included studies were performed years ago; since then, breakpoints of several antibiotics for Enterobacteriaceae have changed, and it is possible that strains that were considered susceptible to non-carbapenem antibiotics at the time of the study were in fact resistant.[43,44] Although carbapenem breakpoints have also decreased,[43] the available data suggest that carbapenems have the lowest MIC values among Enterobacteriaceae.[45–50]

Sixth, in some studies it was impossible to discriminate between patients treated with monotherapy or a combination of antibiotics. In addition, the available data precluded such an analysis because either the proportion of patients receiving combination therapy was negligible or it was not consistently reported as definitive or empirical treatment.[20,21,24,25,27,28] However, there is no clinical evidence thus far that the combination of antibiotics is associated with lower mortality in patients with ESBL-positive bacteraemia.[24,28,33,46]

Publication bias was detected using the funnel plot. It is suggested that the funnel plot should not be used alone; however, for dichotomous outcomes with intervention effects measured as RRs 'the potential problems in funnel plots have been less extensively studied for these effect measures than for ORs, and firm guidance is not yet available as to the model that can be used to explore further a possible asymmetry'.[51]

In conclusion, carbapenems may be considered the treatment of choice for the empirical treatment of patients with ESBL-producing Enterobacteriaceae bacteraemia. BL/BLIs may provide an appropriate, alternative treatment option, and—at least in

some settings—can be used as carbapenem-sparing antibiotics. BL/BLIs can be probably considered effective in definitive therapy for community-associated infections, where the rate of resistance should be considered lower, and in hospital settings with a low level of resistant bacteria. On the other hand, carbapenems should be considered in settings with a high frequency of bacterial resistance or during outbreaks, mainly because of their better *in vitro* activity compared with BL/BLIs. The role of BL/BLIs as definitive treatment for ESBL-positive bacteraemia should be further studied.

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