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Piperacillin-tazobactam vs. carbapenems for treating hospitalized patients with ESBL-producing *Enterobacterales* bloodstream infections: A systematic review and meta-analysis

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ABSTRACT

Objectives: To meta-analyse the clinical efficacy of piperacillin-tazobactam vs. carbapenems for treating hospitalized patients affected by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* bloodstream infections (BSIs).

Methods: Two authors independently searched PubMed-MEDLINE and Scopus database up to January 17, 2024, to retrieve randomized controlled trials (RCTs) or observational studies comparing piperacillin-tazobactam vs. carbapenems for the management of hospitalized patients with ESBL-BSIs. Data were independently extracted by the two authors, and the quality of included studies was independently assessed according to ROB 2.0 or ROBINS-I tools. Mortality rate was selected as primary outcome. Meta-analysis was performed by pooling odds ratios (ORs) retrieved from studies providing adjustment for confounders using a random-effects model with the inverse variance method.

Results: After screening 3,418 articles, 10 studies were meta-analysed (one RCT and nine retrospective observational studies; $N = 1{,}962$). Mortality rate did not significantly differ between treatment with piperacillin-tazobactam vs. carbapenems ($N = 6$; OR: 1.41; 95% CI: 0.96–2.07; $I^2 = 23.6\%$). The findings were consistent also in subgroup analyses assessing patients receiving empirical therapy ($N = 5$; OR: 1.36; 95% CI: 0.99–1.85), or patients having in ≥50% of cases urinary/biliary tract as the primary BSI source ($N = 2$; OR: 1.26; 95% CI: 0.84–1.89). Conversely, the mortality rate was significantly higher with piperacillin-tazobactam only among patients having in <50% of cases urinary/biliary tract as the primary source of BSI ($N = 3$; OR: 2.02; 95% CI: 1.00–4.07).

Conclusions: This meta-analysis showed that, after performing appropriate adjustments for confounders, mortality and clinical outcome in patients having ESBL-producing *Enterobacterales* BSIs did not significantly differ among those receiving piperacillin-tazobactam compared to those receiving carbapenems.

1. Background

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, by exhibiting resistance to most beta-lactam agents, including penicillins, third-generation cephalosporins, and aztreonam, represent a worldwide health concern. Although being detected in several types of gram-negative isolates, ESBLs are currently prevalent among *Escherichia coli, Klebsiella* species, and *Proteus mirabilis* [1]. Various epidemiological studies showed that ESBL-producing *Enterobacterales* may account for up to 35% and 18% of *Klebsiella pneumoniae* and of *E. coli* clinical isolates, respectively [2–4]. Noteworthy, invasive infections caused by ESBL-producing *Enterobacterales* may be burdened by higher mortality rates than those caused by fully susceptible counterparts [5].

What could be better between piperacillin-tazobactam and carbapenems for treating ESBL-producing *Enterobacterales* bloodstream infections (BSIs) still remains a debated issue. On the one hand, the MERINO trial showed that piperacillin-tazobactam did not result in a non-inferior mortality rate compared to meropenem in treating patients with ESBL-producing *Enterobacterales* BSIs [6]. Indeed, the findings of this study were called into ques-

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tion due to some potential bias, namely the lack of pharmacokinetic/pharmacodynamic (PK/PD) optimization of piperacillin-tazobactam therapy and the inclusion of clinical isolates resistant to piperacillin-tazobactam [5,7,8]. On the other hand, it should not be overlooked that an indiscriminate use of carbapenems may favour an ever-growing increase of prevalence of carbapenem-resistant strains, so that carbapenem-sparing strategies based on piperacillin-tazobactam has been advocated [5]. Even the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines and the Infectious Diseases Society of America (IDSA) guidance are not aligned on this issue [9,10]. In this regard, whereas, on the one hand, the ESCMID guidelines recommended the use of old beta-lactam/beta lactamase inhibitor combinations (BL/BLICs) like piperacillin/tazobactam as carbapenem-sparing strategy for treating low-risk non-severe infections [9], on the other hand, the IDSA guidance recommended against piperacillin-tazobactam use for treating infections caused by ESBL-producing *Enterobacterales* outside of the urinary tract.

Although the clinical efficacy of BL/BLICs in the management of ESBL-BSIs was just previously meta-analysed vs. carbapenems in some studies [11–13], none of these assessed neither the outcome after performing appropriate adjustments for confounders nor the unique role of piperacillin-tazobactam.

The aim of this study was to perform a systematic review and meta-analysis of the clinical efficacy of piperacillin-tazobactam vs. carbapenems for treating hospitalized patients with ESBL-producing *Enterobacterales* BSIs after providing adjustment for confounders.

2. Methods

We carried out a systematic review with meta-analysis assessing the clinical efficacy of piperacillin-tazobactam vs. carbapenems in the management of hospitalized patients affected by BSIs due to ESBL-producing *Enterobacterales*. The meta-analysis was registered in the PROSPERO database (CRD42024511077) and conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guideline [14].

2.1. PICO question

Population: Hospitalized patients with BSIs caused by ESBL-producing *Enterobacterales.*

Intervention: Empirical or definitive monotherapy with piperacillin-tazobactam.

Comparator: Empirical or definitive monotherapy with carbapenems.

Outcome: Mortality rate.

2.2. Search strategy

PubMed-MEDLINE and Scopus Database were independently searched by two investigators (MG and PGC) from inception to January 17, 2024, by using the following specific search string: ('piperacillin-tazobactam' OR 'beta-lactam beta-lactamase inhibitor' OR 'meropenem' OR 'carbapenem') AND ('esbl' OR 'extended-spectrum beta-lactamase' OR 'ceftriaxone resistant' OR 'ceftriaxone resistance' OR 'third-generation cephalosporin resistant' OR 'third-generation ceftriaxone resistance') AND ('bloodstream infection' OR 'bacteremia' OR 'bacteraemia' OR 'urinary tract infection' OR 'urosepsis' OR 'pyelonephritis'). No language limitation was adopted. The retrieved records were checked by the same two authors independently for removing eventual duplicates. Reference lists of the included studies were screened for identifying potentially relevant articles.

2.3. Study selection

Selected studies included randomized controlled trials (RCTs) and/or observational studies assessing the clinical outcome of empirical or definitive monotherapy with piperacillin-tazobactam vs. carbapenems on BSIs caused by ESBL-producing *Enterobacterales* in hospitalized patients.

Exclusion criteria were lack of quantitative data for selected outcomes or of adjusted data, absence of a comparator group and presence of BL/BLIs other than piperacillin/tazobactam in the intervention group without subgroup analysis, data coming from conference abstracts or case reports/series.

The primary outcome was in-hospital mortality rate. The secondary outcomes were clinical cure, clinical failure, microbiological eradication and occurrence of breakthrough infections caused by multi-drug resistant (MDR) pathogens.

Screening of titles and abstracts of retrieved records was independently performed by two authors (MG and PGC). Potential discrepancies were resolved by means of discussion between the two authors or consultation with a third reviewer (FP).

2.4. Data extraction

Relevant data of each included study were independently extracted by two authors (MG and PGC) in a prespecified form. Specifically, the following information were retrieved (1) study author and year of publication; (2) study characteristics (study design, country, time period, sample size, exclusion criteria and funding sources); (3) demographics and clinical features of patients included in both intervention and comparator groups; (4) outcome data.

In case of unclear and/or missing data retrieved in the included studies, the corresponding authors would have been contacted for clarification.

2.5. Risk of bias assessment

Risk of bias for each included study was independently evaluated by two investigators (MG and PGC) for the primary outcome. The Cochrane Risk of Bias Tool (RoB 2.0) [15] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) [16] were applied for RCTs and observational studies, respectively. Potential disagreements were discussed with a third reviewer (FP).

2.6. Data synthesis

The impact of using piperacillin-tazobactam vs. carbapenems as empirical or definitive therapy for BSIs due to ESBL-producing *Enterobacterales* on the primary and the secondary outcomes was meta-analysed by pooling adjusted odds ratios (ORs) deriving from the included studies providing adjustment for confounders by means of matched cohorts, propensity score, or multivariate logistic regression analyses. RCTs and observational studies were analysed separately. Treatment effects were calculated as OR, with 95% confidence interval (CI) for dichotomous data, by using a random-effect model with inverse variance method. Significance was assessed by using *t*-test or Z-test for continuous or for dichotomous variables, respectively. A two-sided *P*-value < 0.05 was considered as statistically significant.

Statistical heterogeneity among studies was assessed by means of χ^2 test ($P < 0.10$ indicated significant heterogeneity) and I^2 (>50% indicated substantial heterogeneity). Publication bias was assessed by visual inspection of the funnel plot and Egger's test [17].

Subgroup analyses were performed according to the use of empirical or definitive therapy, the primary source of BSIs (urinary

tract infections [UTI] and biliary infections, defined as at low-intermediate risk [5] with prevalence of ≥50% or <50%), the type of pathogen, the piperacillin-tazobactam MIC values and the low-intermediate risk BSIs as previously defined according to severity at presentation, source of infection and immune status [5]. Sensitivity analysis was conducted according to the risk of bias, by excluding studies at high/critical risk of bias.

Statistical analysis was performed by using MedCalc for Windows (MedCalc statistical software, version 19.6.1, MedCalc Software Ltd, Ostend, Belgium).

3. Results

3.1. Literature search

A total of 3418 potential studies were retrieved, and 3381 out of these were excluded after initial screening of titles and abstracts and searching for duplicates. Overall, 37 full-text articles were considered potentially eligible, and 10 out of these met the final inclusion criteria. The other 27 were excluded because of lack of adjusted outcome data (13 studies), absence of a comparator group (7 studies), inclusion of patients without BSIs (4 studies), and inclusion of patients treated with BL/BLIs without subgroup analysis for piperacillin-tazobactam (3 studies; **Supplementary Fig. 1**).

3.2. Features of the included studies

The 10 included studies consisted of one RCT and nine retrospective observational studies (Table 1) [6,18–26]. Six studies were multicentric [6,20–23,26]. Overall, a total of 1962 patients was enrolled (841 receiving piperacillin-tazobactam vs. 1121 treated with carbapenems). Four studies were conducted in Asia, two in the USA, one in Europe and the other three worldwide.

Median and/or mean age ranged from 48 to 79 years, with a slight male preponderance (ranging from 50.3% to 67%) in all of the included studies. Between 12.5% and 58.7% of patients were immunocompromised, and up to one-third were intensive care unit admitted. In all but one study, piperacillin-tazobactam was administered by intermittent infusion [6,18–21,23–26] (except in [22] by extended infusion over 3 h).

In 5/10 studies, urinary or biliary tract accounted as low-risk primary source of BSI in ≥50% of patients [6,21,22,25,26], whereas they were not represented in one study (all being non-UTI BSIs) [20]. *E. coli* was the most common pathogen in nine out of 10 studies. In the piperacillin/tazobactam group, urinary tract and/or biliary tract represented the most prevalent sources of BSI in seven out of eight studies with available data, with a percentage ranging from 53.0% to 72.9% [6,21–26]. The MIC values of piperacillin-tazobactam were available in four out 10 studies [6,20,25,26]. Specifically, in the piperacillin-tazobactam group the prevalence of ESBL-producing clinical isolates with an MIC value ≤8 mg/L ranged from 89% to 100%.

3.3. Clinical efficacy of piperacillin-tazobactam vs. carbapenems in *ESBL-producing* Enterobacterales *BSIs*

Results of meta-analysis for the primary and the secondary outcomes are reported in Table 2. Seven studies (one RCT and six observational studies) provided data (1571 patients) for assessing the primary outcome [6,18–20,22,23,26]. The mortality rates were investigated at 30-, 14-, or 90-day in five studies [6,18,22,23,26], and in one study each [19,20], respectively. In RCT group, a significant higher risk of mortality rate was found with piperacillin-tazobactam compared to carbapenems (OR: 3.69; 95% CI: 1.54–8.82; $P = 0.003$). In the observational study group, the mortality rate did not significantly differ between piperacillin/tazobactam and carbapenems (OR: 1.41; 95% CI: 0.96–2.07; $P = 0.08$; $I^2 = 23.6\%$; Fig. 1), with no evidence of publication bias ($P = 0.87$).

Two studies (both observational) provided data (73 patients) for assessing clinical failure [24,25]. Clinical failure was defined as persistent bacteraemia (i.e., the presence of a positive blood culture on day 3 or later with no intervening negative blood culture) [24], or as death of all cause by day 14, positive blood culture with ESBL-producing *E. coli* after 2 days from the initiation of piperacillin-tazobactam or carbapenem administration, or no improvement in symptoms related to the infection, including fever (≥37.5°C) by day 7 [25]. Overall, the clinical failure rate did not significantly differ with the use of piperacillin-tazobactam vs. carbapenems (OR: 4.97; 95% CI: 0.25–99.04; $P = 0.29$; $I^2 = 69.5\%$; Fig. 2).

Two studies (one RCT and one observational) provided data (696 patients) for assessing clinical cure [6,21]. Clinical cure was defined as survival plus resolution of fever and leucocytosis plus sterilization of blood cultures at day 4 [6], or as the resolution of all signs and symptoms related to the infection, with no further need for antibiotic therapy [21]. The clinical cure rate did not significantly differ with the use of piperacillin-tazobactam compared to carbapenems both in RCT (OR: 0.74; 95% CI: 0.47–1.16; $P = 0.19$) and in the observational study (OR: 1.02; 95% CI: 0.46–2.27; $P = 0.96$).

Two studies (one RCT and one observational) provided data (529 patients) for assessing the prevalence rate of breakthrough infections caused by MDR pathogens [6,22]. Breakthrough infections caused by MDR pathogens were defined as secondary infections with a meropenem- or piperacillin-tazobactam–resistant organism or *Clostridium difficile* infection [6], or positive clinical cultures of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, carbapenem and/or piperacillin-tazobactam resistant gram-negative bacteria, or other organisms resistant to more than 3 classes of antibiotics and fungal infections within 30 days of index bacteraemia [22]. Overall, the prevalence rate of breakthrough infections caused by MDR pathogens did not significantly differ with carbapenems compared to piperacillin in RCT (OR: 0.50; 95% CI: 0.21–1.21; $P = 0.12$), whereas a significant higher risk was reported with carbapenems in the observational study (OR: 3.32; 95% CI: 1.12–9.87; $P = 0.03$).

No studies provided adjusted data for assessing microbiological eradication.

3.4. Subgroup and sensitivity analyses

The results of the subgroup analyses for the primary outcome are reported in Table 3. In the five studies providing data (1114 patients) for assessing the mortality rate in patients receiving empirical therapy with piperacillin-tazobactam vs. carbapenems [18,19,22,23,26], no significant difference was found between the two groups (OR: 1.36; 95% CI: 0.99–1.85; $I^2 = 0.0\%$; **Supplementary Fig. 2**).

In the two studies providing data for assessing the mortality rate among patients having secondary BSIs originating from UTI/biliary source in ≥50% of cases (563 patients) [22,26], no significant difference between piperacillin-tazobactam and carbapenems emerged (OR: 1.26; 95% CI: 0.84–1.89; $I^2 = 0.0\%$; **Supplementary Fig. 3**). Conversely, in the three studies providing data for assessing the mortality rate among patients having secondary BSIs originating from UTI/biliary source in <50% of cases (516 patients; primary BSIs and pneumonia represented the most prevalent sources of BSI in two [19,23] and one study [20], respectively), a significantly higher risk was found among patients receiving piperacillin-tazobactam vs. carbapenems (OR: 2.02; 95% CI: 1.00–4.07; $I^2 = 26.1\%$; **Supplementary Fig. 4**).

Table 1
Main features of studies included in the meta-analysis.

Study reference	Stud design	Country	Time period	No. of patients (piperacillin/ tazobactam vs. carbapenems)	Age (mean or median)	Male gender	Source of BSI	Isolated pathogens	Severity	Beta-lactam agent and dosing regimen	Adjustment for confounders
Kang et al., 2012 [18]	Retrospective cohort monocentric	Korea	2008–2010	36 vs. 78	NA	NA	NA	68.4% *E. coli* 31.6% *K. pneumoniae*	22.8% haematological malignancies	PTZ Carbapenems not specified	Propensity score (adjustment for confounders was performed, but variables were not specified) Logistic regression model
Tamma et al., 2015 [19]	Retrospective cohort monocentric	USA	2007–2014	103 vs. 110	48.1 vs. 48.2	61.5%	45.5% CR-BSI; 20.7% UTI; 16.9% IAI; 9.4% pneumonia; 8.9% biliary	*E. coli, Klebsiella spp, Proteus spp, S. marcescens*	33.8% ICU admitted; 58.7% immuno-suppressed	103 PTZ (3.375–4.5 g q6h II) 9 ERT (1 g q24h) 4 IMI (500 mg q6h) 97 MER (1–2 g q8h)	Propensity score according to age, Pitt bacteremia score, ICU level care, profound neutropenia (absolute neutrophil count $\leq$ 100 μg/mL), source of infection, underlying medical conditions, and immunocompromised status Cox proportional hazards regression
Ofer-Friedman et al., 2015 [20]	Retrospective cohort multicentric	Israel - USA	2008–2012	10 vs. 69	70.2 ± 16.0	53.0%	100% non-UTI (34% pneumonia; 28% SSTI; 17% biliary; 9% IAI; 12% others)	53.0% *E. coli* 28.0% *K. pneumoniae* 19.0% *P. mirabilis*	28% immuno-suppressed	PTZ ERT IMI MER DOR	Logistic regression model adjusted according to having pneumonia as the infectious clinical syndrome, presence of permanent foreign device, centre, advanced age, deteriorated functional status at admission, and severe sepsis and/or septic shock and/or multiple organ failure
Gutierrez-Gutierrez et al., 2016 [21]	Retrospective cohort multicentric	12 worldwide countries	2004–2013	123 vs. 195	71.5 vs. 66	58.1%	46.0% UTI; 13.4% biliary; 40.6% high-risk source	72.9% *E. coli* 20.3% *K. pneumoniae* 6.8% others	10.7% ICU admitted; 38.1% severe sepsis or septic shock	123 PTZ (4.5 g q6-8h II) 32 ERT 35 IMI 128 MER	Propensity score according to centre, age, gender, underlying conditions, McCabe, acquisition type, source, Pitt score, presentation with severe sepsis or septic shock, and empirical treatment Logistic regression model
Ng et al., 2016 [22]	Retrospective cohort multicentric	Singapore	2012–2013	94 vs. 57	79 vs. 78	50.3%	58.9% UTI; 9.3% biliary; 8.6% pulmonary; 5.3% IAI; 17.9% others	66.9% *E. coli* 33.1% others	8.6% ICU admitted	PTZ 4.5 g q6h II or 4.5 g q8h EI ERT 1 g q24h IMI 500mg q6h MER 1 g q8h	Propensity score according to Pitt bacteraemia score, Charlson's comorbidity index, empiric piperacillin-tazobactam, respiratory BSI source, hepatobiliary BSI source, and unknown BSI source Logistic regression model
Ko et al., 2017 [23]	Retrospective cohort multicentric	Korea	2010–2014	41 vs. 183	63 vs. 61	53.0%	37.1% UTI; 28.0% IAI; 24.1% primary BSI; 3.4% CR-BSI; 7.4% others	68.5% *E. coli* 31.5% *K. pneumoniae*	22.8% haematological malignancies	PTZ carbapenems	Propensity score calculated based on multivariable logistic regression modelling including age, sex, acquisition of infection, UTI, procalcitonin, transfer to ICU within 48 h, APACHE II score, pulmonary disease, and Charlson's score

(*continued on next page*)

Table 1 (*continued*)

Study reference	Stud design	Country	Time period	No. of patients (piperacillin/ tazobactam vs. carbapenems)	Age (mean or median)	Male gender	Source of BSI	Isolated pathogens	Severity	Beta-lactam agent and dosing regimen	Adjustment for confounders
Harris et al., 2018 [6]	RCT	Worldwide (26 centres in 9 countries)	2014–2017	187 vs. 191	70 vs. 69	52.2%	60.9% UTI; 16.4% IAI; 3.2% pulmonary; 3.2% SSTI; 1.6% CR-BSI; 14.7% others	86.5% *E. coli* 13.5% *K. pneumoniae*	7.1% ICU admitted; 24.0% immuno-suppressed	PTZ 4.5 g q6h II MER 1 g q8h	Randomization between treatment arms
Benanti et al., 2019 [24]	Retrospective cohort monocentric	USA	2008–2015	22 vs. 11	54 vs. 52	67%	39.7% IAI; 11.1% CR-BSI; 11.1% pneumonia; 9.5% UTI; 9.5% SSTI; 19.1% unknown	100.0% *E. coli*	100.0% haematological malignancies	PTZ 4.5 g q6h II MER 1 g q8h	Multivariate Cox proportional hazards model and propensity score according to age, gender, Pitt bacteremia score, neutropenia, cancer diagnosis and status, receipt of prior stem cell transplant, current receipt of chemotherapy, the source of infection, and the use of combination aminoglycosides within the first 24 h of culture Logistic regression model
Hoashi et al., 2022 [25]	Retrospective cohort monocentric	Japan	2011–2019	14 vs. 26	69.3 ± 11.2	60.0%	45% UTI; 20% biliary; 15% IAI; 10% liver abscess; 10% others	100.0% *E. coli*	12.5% immuno-suppressed; ICU admitted 2.5%	PTZ Carbapenems	Propensity score according to age, sex, Charlson comorbidity index, McCabe score, solid tumour, haematological malignancy, diabetes mellitus, chronic liver disease, chronic kidney disease, neutropenia, humoral immunosuppression, source of bacteremia, and Pitt bacteremia score
Rando et al., 2024 [26]	Retrospective cohort multicentric	Italy	2018–2022	211 vs. 201	74 vs. 76	53.6%	51.5% UTI; 10.2% biliary; 8.3% IAI; 30.0% others/unknown	100.0% *E. coli*	25.0% immuno-suppressed	PTZ Carbapenems	Propensity score analysis according to age, medical ward stay, surgical ward stay, complicated IAI, BSI source, unknown BSI source, coronary artery disease, heart failure, dementia, leukaemia/lymphoma, chronic obstructive pulmonary disease, liver disease, chronic kidney disease, AIDS and Charlson Comorbidity Index Cox regression model

BSI: bloodstream infection; CR-BSI: catheter-related bloodstream infection; DOR: doripenem; EI: extended infusion; ERT: ertapenem; ESBL: extended-spectrum beta-lactamase; IAI: intrabdominal infection; ICU: intensive care unit; II: intermittent infusion; IMI: imipenem; MER: meropenem; NA: not assessed; PTZ: piperacillin-tazobactam; RCT: randomized controlled trial; SSTI: skin and soft tissue infection; UTI: urinary tract infection.

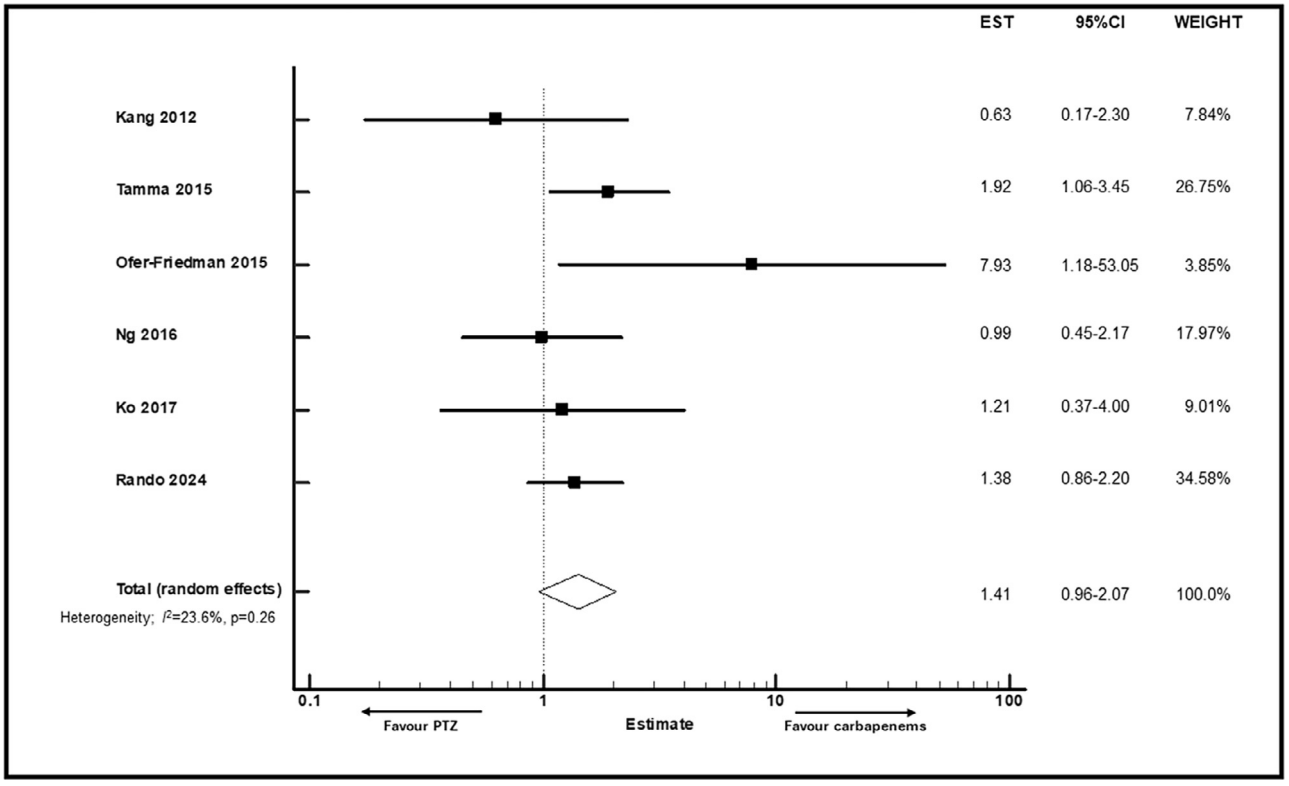

Fig. 1. Forest plot of the adjusted odds ratios (aORs) showing mortality rate in patients with ESBL-producing *Enterobacterales* BSIs receiving piperacillin-tazobactam vs. carbapenems.

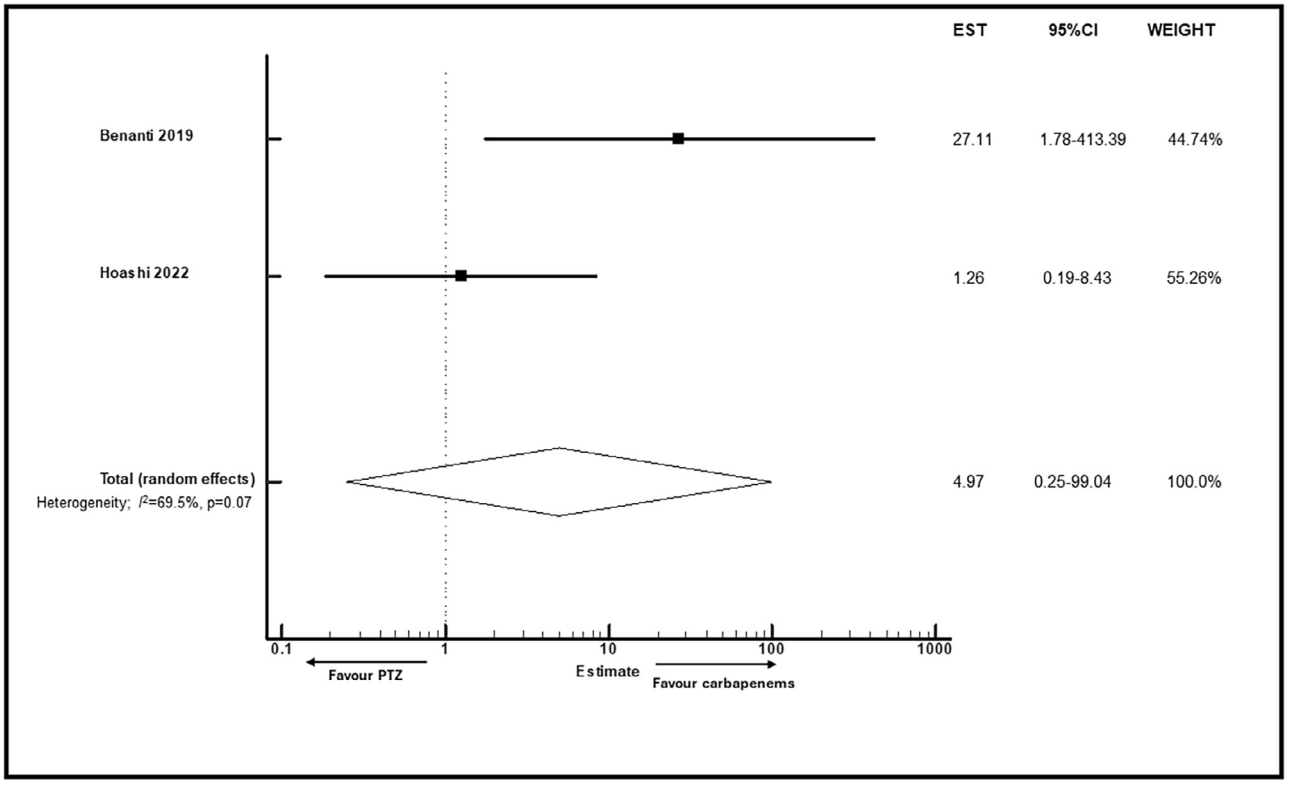

Fig. 2. Forest plot of the adjusted odds ratios (aORs) showing clinical failure rate in patients with ESBL-producing *Enterobacterales* BSIs receiving piperacillin-tazobactam vs. carbapenems.

Table 2
Results of meta-analysis for the primary and the secondary outcomes in patients with ESBL-producing *Enterobacterales* bloodstream infections treated with piperacillin-tazobactam vs. carbapenems.

Outcome	Studies	No. of patients (PTZ vs. carbapenems)	Odds ratio (95% CI)	Heterogeneity (I^2; P value)	Publication bias (P value Egger's test)	Clinical interpretation
Mortality rate (observational studies)	6	495 vs. 698	1.41 (0.96–2.07) $P = 0.08$	23.6% $P = 0.26$	0.87	No significant difference
Mortality rate (RCT)	1	187 vs. 191	3.69 (1.54–8.82) $P = 0.003$	Not applicable	Not applicable	Favour carbapenems
Clinical failure (observational studies)	2	36 vs. 37	4.97 (0.25–99.04) $P = 0.29$	69.5% $P = 0.07$	Not applicable	No significant difference
Clinical cure (observational studies)	1	123 vs. 195	1.02 (0.46–2.27) $P = 0.96$	Not applicable	Not applicable	No significant difference
Clinical cure (RCT)	1	187 vs. 191	0.74 (0.47–1.16) $P = 0.19$	Not applicable	Not applicable	No significant difference
Occurrence of secondary infections caused by MDR pathogens (observational studies)	1	94 vs. 57	3.32* (1.12–9.87) $P = 0.03$	Not applicable	Not applicable	Favour PTZ
Occurrence of secondary infections caused by MDR pathogens (RCT)	1	187 vs. 191	0.50* (0.21–1.21) $P = 0.12$	Not applicable	Not applicable	No significant difference

CI: confidence interval; ESBL: extended-spectrum beta-lactamase; MDR: multidrug-resistant; PTZ: piperacillin-tazobactam.
* Carbapenems vs. piperacillin-tazobactam.

Table 3
Results of subgroup analysis for the primary outcome in patients with ESBL-producing *Enterobacterales* bloodstream infections treated with piperacillin-tazobactam vs. carbapenems.

Subgroup analysis	Studies	No. of patients (PTZ vs. carbapenems)	Odds ratio (95% CI)	Heterogeneity (I^2; P value)	Publication bias (P value Egger's test)	Clinical interpretation
Empirical therapy	5	485 vs. 629	1.36 (0.99–1.85) $P = 0.06$	0.0% $P = 0.50$	0.24	No significant difference
Secondary BSI originating from UTI/biliary source in ≥50% of cases	2	305 vs. 258	1.26 (0.84–1.89) $P = 0.26$	0.0% $P = 0.48$	Not applicable	No significant difference
Secondary BSI originating from UTI/biliary source in <50% of cases	3	154 vs. 362	2.02 (1.00–4.07) $P = 0.05$	26.1% $P = 0.26$	0.68	Favour carbapenems

BSI: bloodstream infection; CI: confidence interval; ESBL: extended-spectrum beta-lactamases; PTZ: piperacillin-tazobactam; UTI: urinary tract infection.

Only one study provided data for assessing the mortality rate in patients receiving definitive therapy (defined as piperacillin-tazobactam or carbapenems monotherapy for ≥50% of treatment duration) [20]. Similarly, only one study provided data for assessing the mortality rate based on the piperacillin-tazobactam MIC values [26]. Conversely, no studies provided adjusted data for assessing the mortality rate based on the type of pathogen or pre-specified criteria of low-intermediate risk.

After excluding studies having serious/critical risk of bias, no significant difference emerged between piperacillin-tazobactam and carbapenems ($n = 7$; OR: 1.29; 95% CI: 0.83–2.00; $I^2 = 55.3\%$).

3.5. Quality of the included studies

In the only RCT included some concerns in deviation from the intended interventions (treating clinicians and investigators were not blinded to treatment allocation) were found (Fig. 3A). One out of the 9 included studies were classified as being at serious risk of bias in at least one domain due to confounding factors, whereas the others were classified as being at moderate risk of bias (Fig. 3B).

4. Discussion

To the best of our knowledge, this is the first meta-analysis that assessed the clinical efficacy of piperacillin-tazobactam compared to carbapenems as empirical or definitive therapy of hospitalized patients with ESBL-producing *Enterobacterales* BSIs after providing adjustment for confounders.

The findings showed that both the mortality rate and the clinical failure rate of hospitalized patients with ESBL-producing *Enterobacterales* BSIs receiving piperacillin-tazobactam were similar to those receiving carbapenems when observational studies providing proper adjustment for confounders were taken into account. Interestingly, subgroup analyses provided consistent results when investigating the role of empirical therapy, as well as that of secondary BSIs originating from the urinary/biliary tract in the majority of cases (namely those with low-intermediate risk primary sources).

Overall, the findings are consistent with those of previous meta-analyses concerning the overall role of various BL/BLICs vs. carbapenems in treating ESBL-producing *Enterobacterales* BSIs [11–13], none of which investigated the role of piperacillin-tazobactam

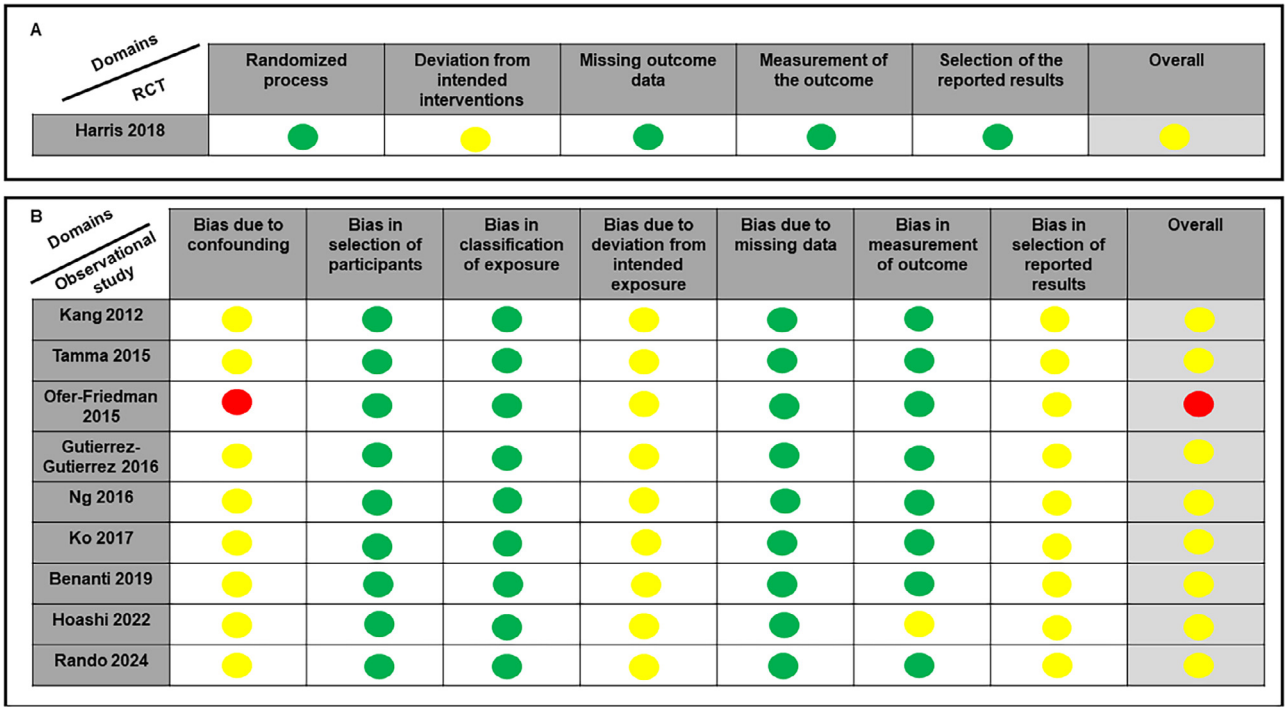

Fig. 3. Risk of bias assessment for RCTs (**A**) and observational studies (**B**) according to ROB 2.0 and ROBINS-I tools.

specifically. Muhammed et al. [11] found no significant difference in mortality rate between carbapenems and BL/BLICs in the empirical (relative risk [RR]: 1.05; 95% CI: 0.83–1.37) and the definitive therapy (RR: 0.62; 95% CI: 0.25–1.52) in 13 and 7 studies, respectively. Sfeir et al. [12] reported no significant difference in mortality rate in 25 observational studies comparing the efficacy of different BL/BLICs and carbapenems in treating patients with ESBL-producing *Enterobacterales* BSIs (OR: 1.07; 95% CI: 0.81–1.82). Zhang et al. [13] reported no significant difference in mortality rate among 1612 patients with ESBL-producing *Enterobacterales* BSIs retrieved from three RCTs and seven observational studies comparing BL/BLICs vs. carbapenems (RR = 0.63; 95% CI: 0.30–1.32). Conversely, they are in contrast with those of the MERINO trial showing that patients having ESBL-producing *Enterobacterales* BSIs treated with piperacillin-tazobactam did not result in a non-inferior mortality rate compared to those having treatment with meropenem [6]. However, some major concerns potentially affecting the study conclusions emerged from this trial [5]. Among the most relevant ones, the choice of not administering piperacillin-tazobactam by CI that would have improved the likelihood of optimal PK/PD target attainment, the inclusion in the analysis also of patients receiving piperacillin-tazobactam despite the identification of clinical isolates resistant to piperacillin-tazobactam, the finding of similar mortality rates occurring in subgroup of patients with a Charlson score < 2, and the presence of some relevant imbalances between the two groups, namely significantly higher proportions, on the one hand, of BSIs secondary to UTI in the meropenem group and, on the other hand, of severely immunocompromised patients in the piperacillin-tazobactam group [5].

In our meta-analysis, the only subgroup analysis showing an increased mortality risk for piperacillin-tazobactam compared to carbapenems was that concerning patients having a low prevalence of urinary/biliary tract as primary source of BSI, namely those having primary BSIs or secondary BSIs originating from pneumonia. This may be explained by the fact that these latter are scenarios usually burdened by high inocula and that piperacillin-tazobactam was generally shown to be more prone to the inoculum effect than meropenem for ESBL-producing *Enterobacterales* [27–30]. Additionally, the limited penetration rate of piperacillin-tazobactam in the epithelial lining fluid could affect the likelihood of optimal PD/PD target attainment, especially when administering the drug by intermittent infusion and dealing with borderline susceptible pathogens [31,32]. Based on this assumption, some opinion articles suggested to avoid the empirical or definitive use of piperacillin-tazobactam whenever dealing with ESBL-producing *Enterobacterales* primary BSIs and/or secondary BSIs originating from pneumonia [5,33].

However, it should not be overlooked another important issue to argue about, namely the fact that the MIC distribution of piperacillin-tazobactam against the ESBL-producing *Enterobacterales* is usually shifted to the right, suggesting less in vitro susceptibility [34,35]. In this regard, currently exist conflicting evidence concerning the association between the MIC values of the clinical isolates for piperacillin-tazobactam and the clinical outcome. Rando et al. [26] found that isolating from patients ESBL-producing *E. coli* with an MIC of 8 mg/L (OR: 2.35; 95% CI: 1.35–3.95) or ≥16 mg/L (OR: 3.69; 95% CI: 1.86–6.91) for piperacillin-tazobactam was an independent predictor of in-hospital 30-day mortality rate. A prospective observational multicentric study including 275 patients receiving piperacillin-tazobactam for treating BSIs due to *Enterobacterales* (248 exhibiting piperacillin-tazobactam MIC values ≤4 mg/L and 27 with MIC values of 8–16 mg/L) found no significant impact of borderline MIC values on clinical outcome [36]. Conversely, a retrospective observational study including 10,101 hospitalized patients receiving piperacillin-tazobactam for treating *Enterobacterales* infections reported no significant difference in mortality rate between isolates with low (≤4 mg/L) vs. intermediate (8–16 mg/L) MIC values [37]. Consequently, it may be hypothesized that having clinical isolates with borderline susceptibility may affect the likelihood of PK/PD target attainment of piperacillin-tazobactam against ESBL-producing *Enterobacterales* especially when adopting traditional intermittent infusion administration. Interestingly, intermittent infusion administration was adopted in all but one [22] of the studies included in

our meta-analysis. It should be mentioned that extended-infusion (EI) or continuous-infusion (CI) administration was shown to maximize aggressive joint PK/PD target attainment with piperacillin-tazobactam under the same daily dose [38,39]. This administration modality has been associated with both maximization of clinical efficacy and suppression of resistance emergence in treating gram-negative infections [40–43]. Interestingly, a recent prospective study assessed the relationship between aggressive joint PK/PD target attainment of CI piperacillin-tazobactam monotherapy and microbiological outcome among 35 patients with ESBL-producing *Enterobacterales* secondary BSIs originating from the urinary or the biliary/abdominal source and undergoing real-time therapeutic drug monitoring [44]. Noteworthy, optimal PK/PD target with CI piperacillin-tazobactam was attained is as much as 97.1% of cases and resulted in microbiological eradication in as much as 91.4% of cases [44]. This could allow to speculate that this strategy could be helpful even when dealing with piperacillin-tazobactam against ESBL-producing *Enterobacterales* primary BSIs, but clearly this hypothesis has to be tested in prospective studies before drawing any potential conclusion.

Overall, the findings may support the use of piperacillin-tazobactam in the challenging scenario of ESBL-producing *Enterobacterales* BSIs. Notably, the most suitable and reliable scenario should be that of the immunocompetent host having non-severe secondary BSI originating from low-intermediate risk primary sources, as previously suggested [5,44]. Administration by CI may increase the likelihood of attaining aggressive PK/PD target against ESBL-producing *Enterobacterales*. This may represent a valuable carbapenem-sparing strategy for limiting the ever growing prevalence of carbapenem-resistant gram-negative isolates, while waiting for novel BL/BLICs more efficacious against ESBL-producing *Enterobacterales*, namely cefepime-enmetazobactam [45,46].

Limitations of our meta-analysis must be acknowledged. Most of the included studies had a retrospective design and limited sample size, no subgroup analysis investigating specific pathogens or infection site was feasible due to lacking data, and the potential role of other unmeasured confounders cannot be ruled out. Conversely, including studies providing adjustment for confounders could have minimized residual biases and the finding of no difference with carbapenems despite intermittent infusion administration in the vast majority of included studies may represent points of strength.

In conclusion, the meta-analysis showed that, after performing appropriate adjustments for confounders, mortality and clinical outcome in patients having ESBL-producing *Enterobacterales* BSIs did not significantly differ among those receiving piperacillin-tazobactam compared to those receiving carbapenems. Further prospective studies addressing the issue of improved PK/PD target attainment of piperacillin-tazobactam based on EI or CI dosing regimens are warranted for confirming and strengthening the findings.

Author contributions

MG: conceptualization, data curation, formal analysis and writing original draft; PGC: data curation and formal analysis; FP: conceptualization, data curation and review and editing of final manuscript.

Declarations

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2024.08.002.

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