TRENDS IN SCIENCES 2025; 22(8): 9681

https://doi.org/10.48048/tis.2025.9681

REVIEW ARTICLE

Comparative Effectiveness of Single, Dual, and Multi-Antibiotic Therapies in Managing Carbapenem-Resistant *Enterobacterales*: A Systematic Review and Meta-Analysis on Survival Rates

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Received: 31 December 2024, Revised: 10 February 2025, Accepted: 5 March 2025, Published: 20 June 2025

Abstract

Carbapenem-resistant *Enterobacterales* (CRE) represent a major global health issue, linked to elevated rates of morbidity and mortality stemming from restricted treatment alternatives. The Gram-negative bacteria, such as *Klebsiella pneumoniae* and *Escherichia coli*, are significant contributors to severe infections, including bacteremia, pneumonia, and urinary tract infections. Mechanisms of resistance such as the production of carbapenemases, the action of efflux pumps, and mutations in porins diminish the effectiveness of carbapenems, which are frequently the antibiotics of last resort. In light of this escalating concern, the absence of a universally recognized global guideline for the management of CRE results in diverse treatment strategies. This systematic review and meta-analysis aimed to evaluate the effectiveness of monotherapy, dual therapy, and multi-antibiotic regimens in the treatment of CRE infections. In accordance with established guidelines, data from 5 major databases were analyzed, and the quality of the studies was evaluated using the Newcastle-Ottawa Scale. The findings indicated that combination therapy led to a notable enhancement in survival rates when contrasted with monotherapy (OR = 0.69, 95 % CI 0.62 - 0.78, $p < 0.00001$). In contrast, no significant difference was found between dual therapy and multi-antibiotic regimens (OR = 1.17, 95 % CI 0.95 - 1.46, $p = 0.15$). The combination therapy exhibited synergistic effects, improving bacterial eradication while reducing the emergence of resistance. Dual therapy demonstrated superior outcomes when contrasted with multi-antibiotic regimens, presenting lower toxicity risks and enhanced patient adherence. Nonetheless, the absence of stratification considering resistance mechanisms, infection severity, and patient characteristics highlights the necessity for tailored treatment strategies. In conclusion, this study emphasizes the critical necessity for internationally standardized protocols for CRE management to guarantee uniform and effective treatment. Future investigations should concentrate on resistance profiling, assessing the safety and cost-effectiveness of dual and multi-antibiotic regimens, and customizing therapies to individual patient factors to enhance outcomes.

Keywords: Antibiotic, Combination therapy, *Enterobacterales*, Monotherapy, Survival rate

Introduction

Infections caused by *Enterobacterales* represent a significant global health issue, particularly due to the prevalence of carbapenem-resistant *Enterobacterales*. *Enterobacterales*, an ordo of gram-negative bacteria, is associated with several diseases in humans and animals, such as bacteremia, pulmonary infections, and urinary tract infections [1]. Carbapenem-resistant *Enterobacterales* (CRE) have emerged as a substantial public health concern, causing significant morbidity and mortality in hospital settings [2,3]. A meta-analysis revealed a global prevalence of carbapenem-resistant *Enterobacterales* (CRE) at 43.06 %, with *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae* as the predominant species [4]. A further analysis revealed carbapenem resistance in 31.4 % of *Escherichia coli* and 25.8 % of *Klebsiella pneumoniae* isolates [5]. Infections caused by

Enterobacterales are prevalent in children, with *Escherichia coli* representing 47.69 % of cases, followed by *Salmonella* at 24.62 % and *Klebsiella* at 15.38 % [6]. Urinary tract infections were the predominant symptoms in both adults and children [5,6].

Infections caused by carbapenem-resistant *Enterobacterales* (CRE) are linked to markedly elevated death rates in contrast to infections from carbapenem-susceptible *Enterobacterales* (CSE), attributable to restricted treatment alternatives [7-10]. CRE infections provide a 3.39-fold increased risk of total death compared to CSE infections [9]. Carbapenems are last-resort antibiotics extensively employed to address bacterial infections caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales*. Consequently, if a bacterial strain exhibits resistance to this antibiotic, it will pose significant challenges [11]. *Klebsiella pneumoniae* and *Escherichia coli* are the principal etiological agents of CRE infections, employing resistance mechanisms including enzyme production, efflux pumps, and porin mutations [12,13]. Carbapenemases encompass KPC, MBLs, and OXA-48-like enzymes that disseminate rapidly via plasmids [13].

The fast worldwide proliferation of carbapenemase-producing *Enterobacterales* needs immediate investigation to identify effective treatments [2,13]. Current therapy comprise polymyxins, tigecycline, fosfomycin, and aminoglycosides [8]. Combination treatment of 2 or more pharmacological agents has demonstrated enhanced efficacy relative to monotherapy [14]. For carbapenem-resistant Enterobacteriaceae (CRE) with carbapenem minimum inhibitory concentrations (MICs) $\leq$ 8 mg/L, the combination of carbapenems with colistin, high-dose tigecycline, or aminoglycosides may be efficacious [15]. Recently introduced antibiotics, including ceftazidime-avibactam, meropenem-vaborbactam, plazomicin, and eravacycline, provide supplementary alternatives for the treatment of CRE [7,8]. Additional interesting pharmaceuticals under research are imipenem-relebactam and cefiderocol [8]. Strategies to address CRE including repurposing existing antibiotics, combining antibiotic therapies, or are seen as viable approaches in [13]. Treatment techniques must be tailored according to resistance mechanisms, susceptibility profiles, illness severity, and patient characteristics [7,8].

To address the lack of a widely recognized worldwide protocol for the management of carbapenem-resistant *Enterobacterales* (CRE) infections, considering their considerable global health impact and correlation with elevated morbidity and death rates. This study aims to assess the relative efficacy of monotherapy, dual therapy, and multiple antibiotic regimens as reported in observational studies, offering essential insights into treatment alternatives customized to CRE infection as a consideration in the clinical setting.

Materials and methods

Study methodology

This meta-analysis and systematic review were performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol for this review has been registered in PROSPERO under ID Number CRD42024629626. The independent variable consisted of the type of antibiotic therapy (dual-antibiotic or multi-antibiotic therapy compared to single-antibiotic therapy), whereas the dependent variable was the survival rates of patients with CRE infections.

Eligibility criteria

The inclusion criteria were established utilizing the PICOS framework. The criteria for study inclusion are as follows: (1) the population comprises patients with Carbapenem-Resistant *Enterobacterales* (CRE) infections; (2) the intervention entails dual-antibiotic therapy and multi-antibiotic therapy; (3) comparator groups consist of populations receiving single antibiotic therapy; (4) outcome measures focus on survival rates; (5) the study design is observational studies. The exclusion criteria are: (1) irrelevant outcomes; (2) insufficient data; and (3) irretrievable studies.

Data sources and search strategies

The literature search was conducted on December 14, 2024, utilizing the following databases: PubMed, Cochrane CENTRAL, ScienceDirect, Scopus, and EBSCOhost. Search keywords were developed in line with the MeSH (Medical Subject Headings) browser and integrated using Boolean operators. The keywords used included: *("Enterobacterales" OR "Enterobacteriaceae" OR "Escherichia coli" OR "Proteus mirabilis" OR Enterobacter OR "Serratia marcescens" OR*

"Citrobacter" OR "Klebsiella") AND ("ESBL" OR "Beta lactamase" OR "β-lactamase") AND ("Monotherapy" OR "Mono" OR "Combination") AND ("Antibiotic") AND ("Cohort" OR "Case control" OR "Retrospective" OR "Observational") AND (Survive OR Survival OR Died OR Mortality OR Death). The search details for each database can be seen in **Table S1**.

Study selection results

Three independent reviewers (MFH, DEP and SAA) will apply the eligibility criteria and select studies for inclusion in the systematic review and meta-analysis. All studies from databases were collected in Rayyan.ai (Rayyan Systems Inc., Doha, Qatar). All collected articles were screened for year, title, and abstract by 3 independent reviewers after duplicates were removed. Each reviewer will independently screen the titles and abstracts of identified records and select potentially relevant studies. Full texts of these potentially relevant studies will then be retrieved and independently assessed for eligibility by both reviewers. The reviewers will be blinded to each other's decisions during this process. Any disagreements between the reviewers during the study selection process will be resolved through discussion until consensus is reached. If consensus cannot be reached, a fourth reviewer (ES) will be consulted.

Data extraction

The data obtained from the chosen studies comprised the author's name and publication year, sample size in the intervention group, sample size in the control group, age, treatment regimens, type of infection, type of bacteria, and duration of observation. Survival rate data were extracted for each study.

Study quality and risk of bias

The studies obtained were subsequently evaluated for quality and risk of bias. Fifty-one studies were evaluated utilizing the Newcastle-Ottawa Score (NOS). Bias assessment encompasses 3 primary domains: selection, comparability, and outcome in cohort studies, as well as exposure in case-controlled studies. Each domain comprises multiple criteria, with a maximum score of 9 points representing the highest quality. Selection, scoring up to 4 points, evaluates the representativeness of research groups and the participant selection method. This includes assessing the representativeness of cases or exposed groups, the source of controls, and the validation of exposure through reliable data. Comparability, with a scoring range of up to 2 points, assesses the extent to which the study addresses confounding variables. Points are awarded for the consideration of relevant factors that may impact the study's findings, facilitating a balanced comparison. The outcome or exposure, which can receive a maximum of 3 points, evaluates the quality of outcome assessment in cohort studies or exposure ascertainment in case-control studies. This includes considerations of follow-up adequacy, consistency in outcome measurement, and bias reduction. Research exhibiting elevated NOS scores, reaching a maximum of 9 points, is deemed to possess a reduced risk of bias and enhanced methodological quality.

Quantitative data synthesis (meta-analysis)

Statistical analysis was conducted using Review Manager 5.4.1. (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). We will use a random-effects meta-analysis to combine individual study data, given the likely clinical and methodological diversity among the included studies. This approach assumes that the true effect size varies from study to study and provides a more conservative estimate of the effect size and its confidence interval.

The type of data used is dichotomous and the outcomes will be synthesized using odds ratio (OR) with a 95 % Confidence Interval (CI). If heterogeneity is low, the meta-analysis forest plot will use a fixed effect model. The I^2 statistic will be calculated to evaluate the degree of heterogeneity, ranging from 0 to 100 %, indicating the extent of heterogeneity from none to high. Typically, an I^2 value greater than 50 % indicates moderate to high heterogeneity. Meta-regression towards age was conducted using Comprehensive meta-analysis v3.

Results and discussion

Study selection and quality assessment

After the search process in 5 databases, 1,023 articles were collected. A total of 267 duplicate articles, were removed. leaving 756 articles for manual selection based on title and abstract. A total of 532 articles were excluded because they met the exclusion criteria or did not meet the inclusion criteria by reading the title and abstract. This left 224 articles to be accessed but only 84 articles that can only read in full-text for the comprehensive assessment. A total of 28 articles had irrelevant outcome and insufficiency data in 5 articles. The final results were 51 studies, which were included in the quantitative synthesis. The flow of article searches and study selection can be seen in the PRISMA 2020 diagram in **Figure 1**.

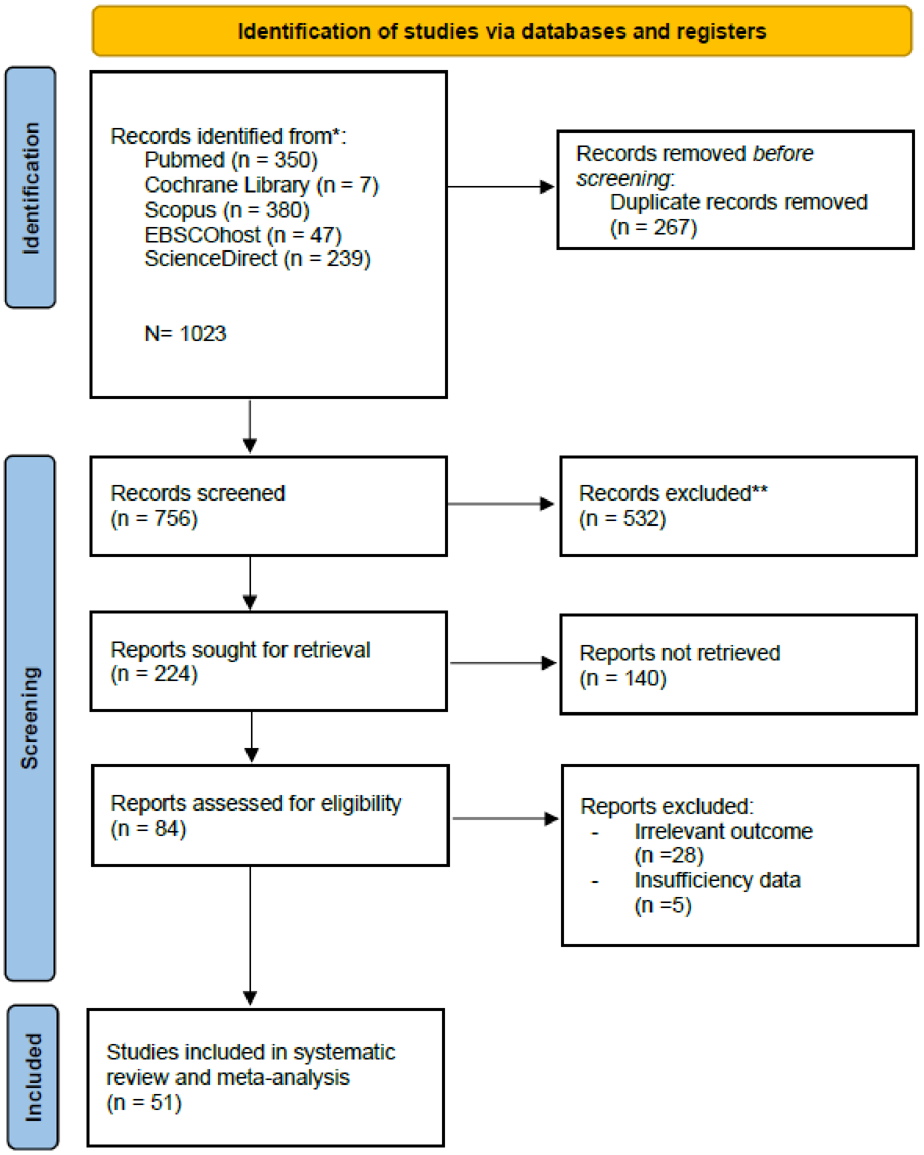
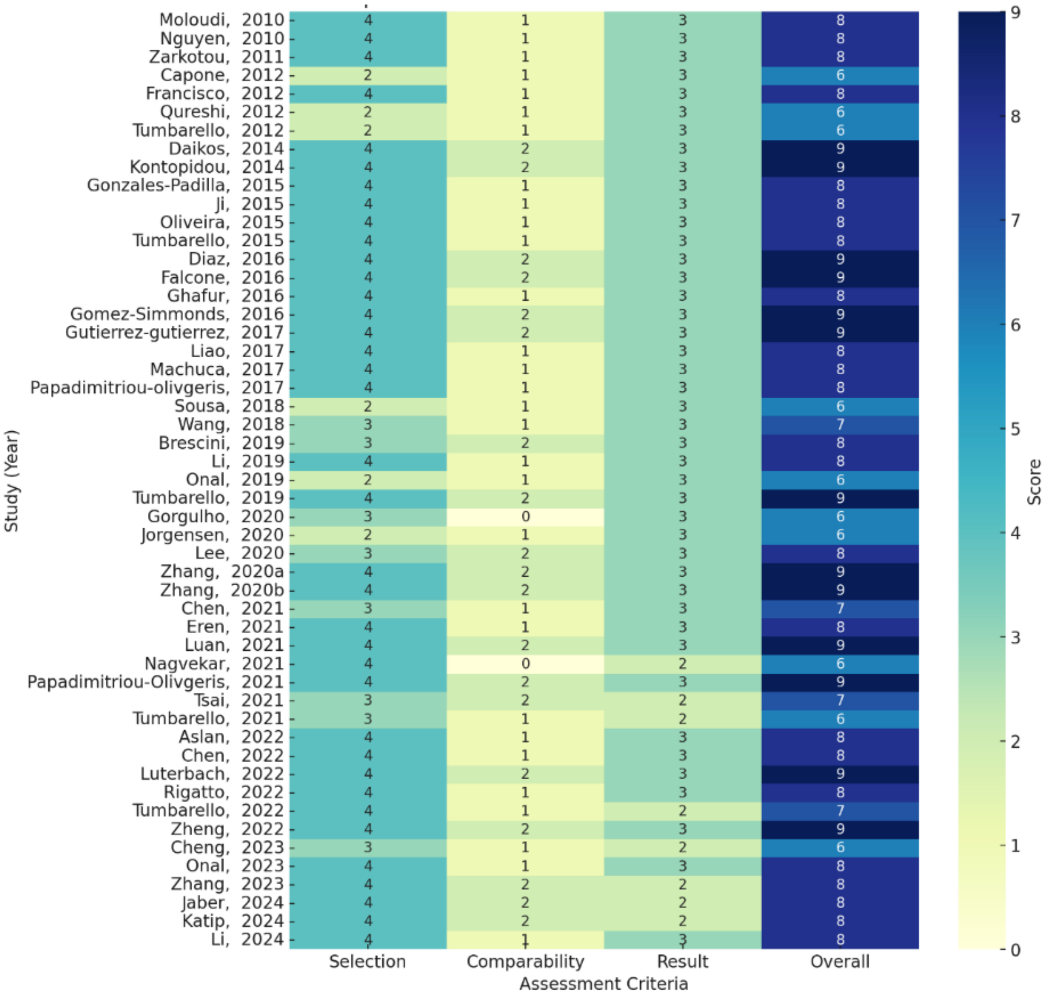


Figure 1 Prisma 2020 diagram.

According to **Figure 2**, the predominant overall score among studies is 8, with 9 being the second most prevalent score. A limited number of studies indicate scores of 6 and 7. Research with elevated scores (8 - 9) exhibits a decreased risk of bias, as it reflects more robust selection methodologies, enhanced comparability among groups, and more explicit result reporting. Research with lower scores (6 - 7) may exhibit an elevated risk of bias (moderate risk of bias), possibly because to insufficient control of confounding factors or methodological deficiencies. The majority of research in this study exhibits low to moderate bias risk, suggesting that their results are generally trustworthy; nevertheless, certain studies may necessitate more careful interpretation. Thirty-seven inclusion studies demonstrated a low risk of bias, while the remaining studies exhibited a moderate risk of bias. This suggests that the evidence quality in this review is relatively high.



Study (Year)	Selection	Comparability	Result	Overall
Moloudi, 2010	4	1	3	8
Nguyen, 2010	4	1	3	8
Zarkotou, 2011	4	1	3	8
Capone, 2012	2	1	3	6
Francisco, 2012	4	1	3	8
Qureshi, 2012	2	1	3	6
Tumbarello, 2012	2	1	3	6
Daikos, 2014	4	2	3	9
Kontopidou, 2014	4	2	3	9
Gonzales-Padilla, 2015	4	1	3	8
Ji, 2015	4	1	3	8
Oliveira, 2015	4	1	3	8
Tumbarello, 2015	4	1	3	8
Diaz, 2016	4	2	3	9
Falcone, 2016	4	2	3	9
Ghafur, 2016	4	1	3	8
Gomez-Simmonds, 2016	4	2	3	9
Gutierrez-gutierrez, 2017	4	2	3	9
Liao, 2017	4	1	3	8
Machuca, 2017	4	1	3	8
Papadimitriou-olivgeris, 2017	4	1	3	8
Sousa, 2018	2	1	3	6
Wang, 2018	3	1	3	7
Brescini, 2019	3	2	3	8
Li, 2019	4	1	3	8
Onal, 2019	2	1	3	6
Tumbarello, 2019	4	2	3	9
Gorgulho, 2020	3	0	3	6
Jorgensen, 2020	2	1	3	6
Lee, 2020	3	2	3	8
Zhang, 2020a	4	2	3	9
Zhang, 2020b	4	2	3	9
Chen, 2021	3	1	3	7
Eren, 2021	4	1	3	8
Luan, 2021	4	2	3	9
Nagvekar, 2021	4	0	2	6
Papadimitriou-Olivgeris, 2021	4	2	3	9
Tsai, 2021	3	2	2	7
Tumbarello, 2021	3	1	2	6
Aslan, 2022	4	1	3	8
Chen, 2022	4	1	3	8
Luterbach, 2022	4	2	3	9
Rigatto, 2022	4	1	3	8
Tumbarello, 2022	4	1	2	7
Zheng, 2022	4	2	3	9
Cheng, 2023	3	1	2	6
Onal, 2023	4	1	3	8
Zhang, 2023	4	2	2	8
Jaber, 2024	4	2	2	8
Katip, 2024	4	2	2	8
Li, 2024	4	1	3	8

Figure 2 NOS score of risk assessment.

Studies characteristics

A total of 6,545 participants, aged 18 to 76 years, were included from the 51 articles, encompassing patients with CRE infections. The interventions employed consist of single antibiotic therapy, dual-antibiotic therapy, and multi-antibiotic therapy, with observation periods spanning 14 to 30 days. Detailed tables of study characteristics can be seen in **Table S2**. Research indicates that elderly patients in intensive care units exhibit a diminished immune response, with Gram-negative bacteria identified as the primary agents of bloodstream infections in this population, characterized by elevated antibiotic resistance levels [67]. This statement parallels the findings of the study, which involved predominantly middle-aged to elderly patients (45 - 74 years old) suffering from bloodstream infections. Long-term care facilities frequently act as reservoirs for bacteria that exhibit resistance to multiple drugs, thereby increasing patients' susceptibility to bacterial infections, including carbapenem-resistant *Klebsiella pneumoniae* [68]. This finding aligns with the study, which indicated that most patients were ICU patients infected with *Klebsiella pneumoniae*.

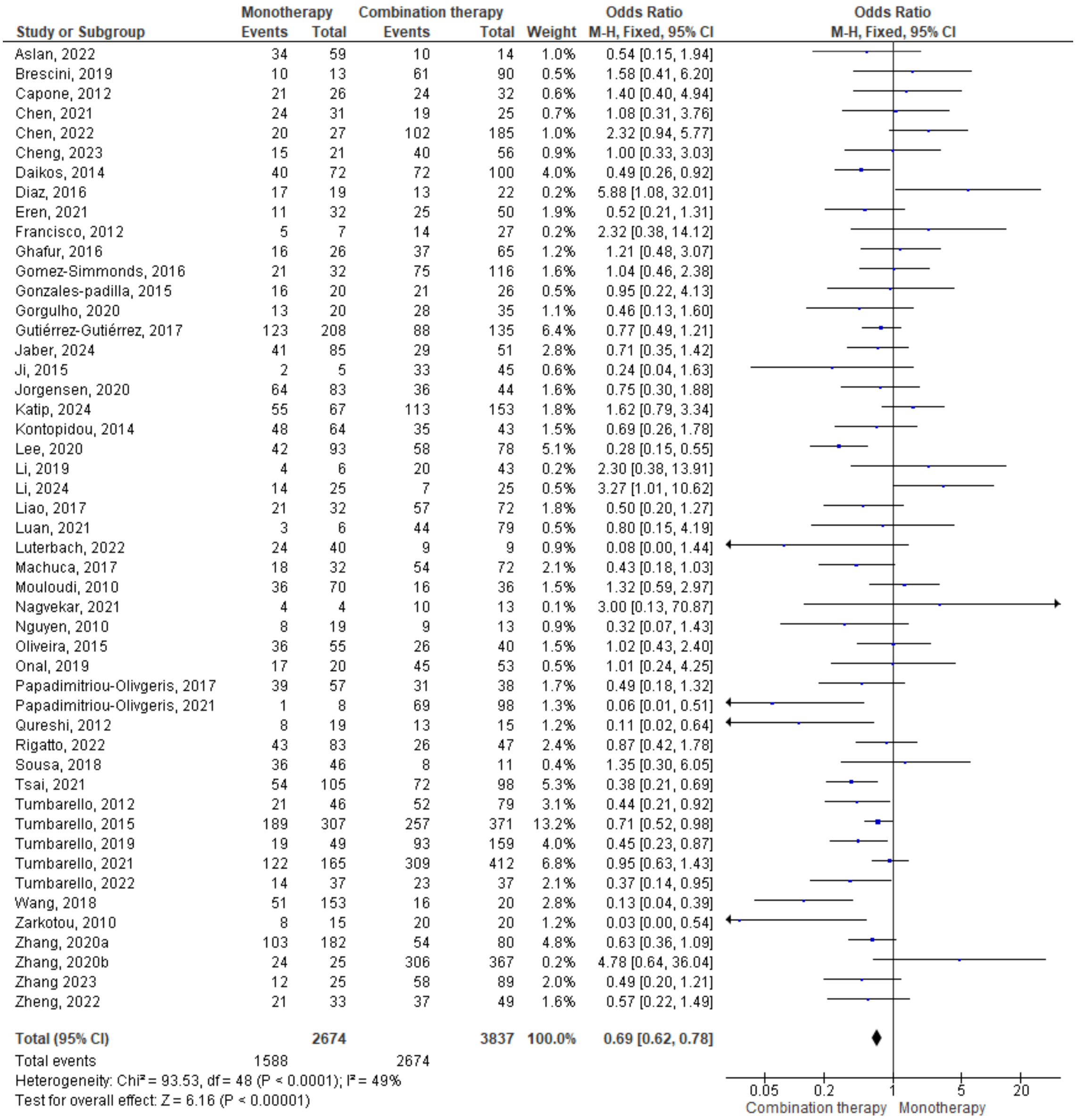
Meta-analysis and meta-regression on patients age

Comparison of monotherapy and combination therapy antibiotic treatments indicates that 3combination therapy is superior regarding the survival rate of patients infected with CRE (**Figure 3**). The meta-analysis results indicate that combination therapy significantly enhances the survival rate (OR = 0.69, 95 % CI (0.62, 0.78), p < 0.00001, I^2 = 49 %) in comparison to antibiotic monotherapy. The results are corroborated by a low level of heterogeneity (I^2 = 49 %), suggesting that the variations among studies are minimal, thereby affirming the reliability and consistency of the meta-analysis finding [69].

In accordance with the results of our meta-analysis, several studies also indicate that combination therapy offers superior treatment benefits compared to monotherapy, as it enhances efficacy and decreases the risk of resistance, resulting in improved mortality outcomes [70,71]. Combination antibiotic therapy provides synergistic effects through the use of multiple drugs with diverse mechanisms of action, enhancing efficacy against resistant bacteria and decreasing the probability of resistance emergence [70,72]. Combination therapy, which employs 2 or more antibiotics targeting distinct mechanisms within bacterial cells, can achieve a synergistic effect, leading to a more comprehensive therapeutic outcome [73,74]. The combined effects lead to bacteria experiencing effective mutations against all agents simultaneously, a mechanism that is infrequently observed in antibiotic monotherapy [70]. Combination therapy enhances the effectiveness of drugs, leading to improved therapeutic success and higher patient recovery rates, which in turn reduces mortality rates [75]. The findings align with Schmid *et al.* [71], which indicated that combination therapy reduced mortality in infections caused by resistant gram-negative bacteria, especially in bloodstream infections and those involving carbapenemase-producing *Enterobacterales*.

This study identifies CTN+TGC (Colistin + Tigecycline) as the most prevalent drug combination, with TGC + CBM (Tigecycline + Carbapenem) following closely behind. Numerous studies demonstrate the efficacy of these drug combinations. Zhou *et al.* [76] demonstrated that the combination of CTN and TGC produced significant effects compared to monotherapy with either drug, effectively reducing the density of carbapenem and colistin-resistant *E. coli* within 48 h. Cai *et al.* [77] reported that the combination of CTN and TGC led to a greater reduction in bacterial density and significantly decreased the area under the bactericidal curve compared to colistin alone. The combination of TGC and CBM has been shown to produce superior effects compared to monotherapy. Fergadaki *et al.* [78] demonstrated that the combination of tigecycline and meropenem displayed superior bactericidal activity relative to monotherapy, particularly against carbapenemase-producing *Klebsiella pneumoniae* isolates. This combination effectively reduced bacterial load in tissues and enhanced survival rates in experimental infection models. Combination therapy utilizing carbapenems and tigecycline demonstrates greater efficacy than monotherapy in decreasing mortality rates among patients with pneumonia infections [72].

This study identifies colistin and tigecycline as the most prevalent monotherapy regimens. In contrast to the outcomes of combination therapy, monotherapy is frequently linked to reduced clinical and microbiological success rates when compared to combination therapy [79]. Wang *et al.* [80] demonstrated that monotherapy with Tigecycline resulted in a mortality rate 2.73 times greater than that of tigecycline-based combination therapy for bloodstream infections. A study by Cheng *et al.* [81] indicated that monotherapy with colistin was associated with a 1.03 times higher mortality risk ratio compared to combination therapy with colistin in infections caused by carbapenem-resistant gram-negative bacteria. Monotherapy is frequently inadequate for treating infections caused by multidrug-resistant (MDR), extensively drug-resistant (XDR), or pan-drug-resistant (PDR) bacteria, as it lacks the necessary broad spectrum to address these infections [72,79].

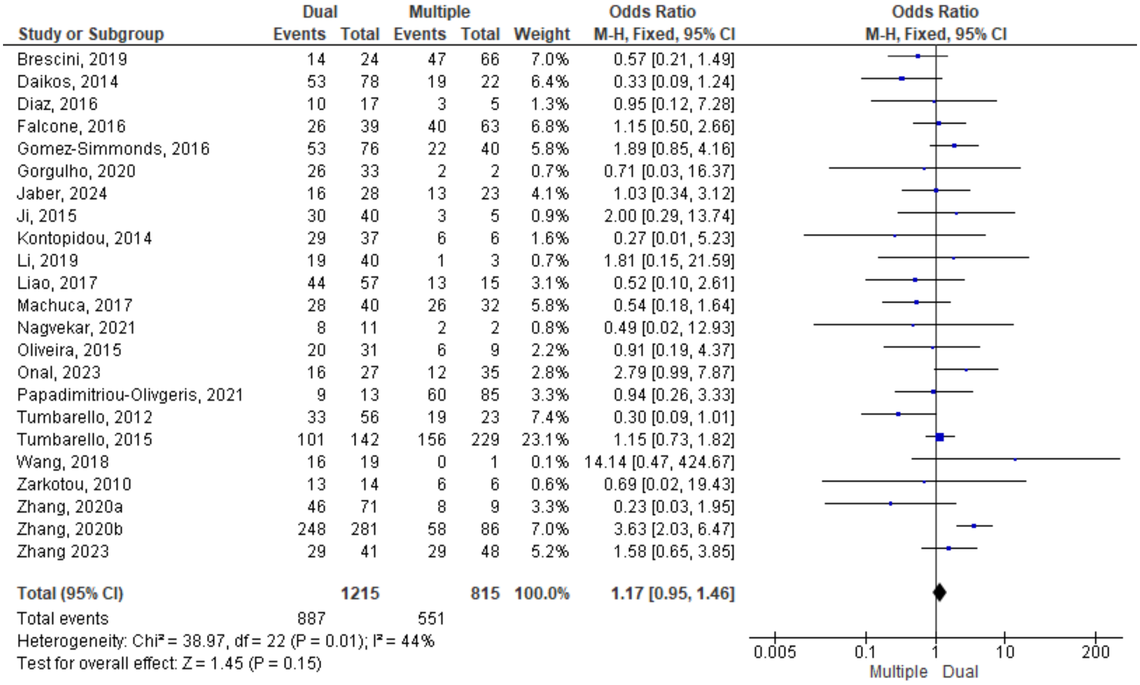


	Monotherapy		Combination therapy			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Aslan, 2022	34	59	10	14	1.0%	0.54 [0.15, 1.94]
Brescini, 2019	10	13	61	90	0.5%	1.58 [0.41, 6.20]
Capone, 2012	21	26	24	32	0.6%	1.40 [0.40, 4.94]
Chen, 2021	24	31	19	25	0.7%	1.08 [0.31, 3.76]
Chen, 2022	20	27	102	185	1.0%	2.32 [0.94, 5.77]
Cheng, 2023	15	21	40	56	0.9%	1.00 [0.33, 3.03]
Daikos, 2014	40	72	72	100	4.0%	0.49 [0.26, 0.92]
Diaz, 2016	17	19	13	22	0.2%	5.88 [1.08, 32.01]
Eren, 2021	11	32	25	50	1.9%	0.52 [0.21, 1.31]
Francisco, 2012	5	7	14	27	0.2%	2.32 [0.38, 14.12]
Ghafur, 2016	16	26	37	65	1.2%	1.21 [0.48, 3.07]
Gomez-Simmonds, 2016	21	32	75	116	1.6%	1.04 [0.46, 2.38]
Gonzales-padilla, 2015	16	20	21	26	0.5%	0.95 [0.22, 4.13]
Gorgulho, 2020	13	20	28	35	1.1%	0.46 [0.13, 1.60]
Gutiérrez-Gutiérrez, 2017	123	208	88	135	6.4%	0.77 [0.49, 1.21]
Jaber, 2024	41	85	29	51	2.8%	0.71 [0.35, 1.42]
Ji, 2015	2	5	33	45	0.6%	0.24 [0.04, 1.63]
Jorgensen, 2020	64	83	36	44	1.6%	0.75 [0.30, 1.88]
Katip, 2024	55	67	113	153	1.8%	1.62 [0.79, 3.34]
Kontopidou, 2014	48	64	35	43	1.5%	0.69 [0.26, 1.78]
Lee, 2020	42	93	58	78	5.1%	0.28 [0.15, 0.55]
Li, 2019	4	6	20	43	0.2%	2.30 [0.38, 13.91]
Li, 2024	14	25	7	25	0.5%	3.27 [1.01, 10.62]
Liao, 2017	21	32	57	72	1.8%	0.50 [0.20, 1.27]
Luan, 2021	3	6	44	79	0.5%	0.80 [0.15, 4.19]
Luterbach, 2022	24	40	9	9	0.9%	0.08 [0.00, 1.44]
Machuca, 2017	18	32	54	72	2.1%	0.43 [0.18, 1.03]
Mouloudi, 2010	36	70	16	36	1.5%	1.32 [0.59, 2.97]
Nagvekar, 2021	4	4	10	13	0.1%	3.00 [0.13, 70.87]
Nguyen, 2010	8	19	9	13	0.9%	0.32 [0.07, 1.43]
Oliveira, 2015	36	55	26	40	1.5%	1.02 [0.43, 2.40]
Onal, 2019	17	20	45	53	0.5%	1.01 [0.24, 4.25]
Papadimitriou-Olivgeris, 2017	39	57	31	38	1.7%	0.49 [0.18, 1.32]
Papadimitriou-Olivgeris, 2021	1	8	69	98	1.3%	0.06 [0.01, 0.51]
Qureshi, 2012	8	19	13	15	1.2%	0.11 [0.02, 0.64]
Rigatto, 2022	43	83	26	47	2.4%	0.87 [0.42, 1.78]
Sousa, 2018	36	46	8	11	0.4%	1.35 [0.30, 6.05]
Tsai, 2021	54	105	72	98	5.3%	0.38 [0.21, 0.69]
Tumbarello, 2012	21	46	52	79	3.1%	0.44 [0.21, 0.92]
Tumbarello, 2015	189	307	257	371	13.2%	0.71 [0.52, 0.98]
Tumbarello, 2019	19	49	93	159	4.0%	0.45 [0.23, 0.87]
Tumbarello, 2021	122	165	309	412	6.8%	0.95 [0.63, 1.43]
Tumbarello, 2022	14	37	23	37	2.1%	0.37 [0.14, 0.95]
Wang, 2018	51	153	16	20	2.8%	0.13 [0.04, 0.39]
Zarkotou, 2010	8	15	20	20	1.2%	0.03 [0.00, 0.54]
Zhang, 2020a	103	182	54	80	4.8%	0.63 [0.36, 1.09]
Zhang, 2020b	24	25	306	367	0.2%	4.78 [0.64, 36.04]
Zhang 2023	12	25	58	89	2.0%	0.49 [0.20, 1.21]
Zheng, 2022	21	33	37	49	1.6%	0.57 [0.22, 1.49]
Total (95% CI)		**2674**		**3837**	**100.0%**	**0.69 [0.62, 0.78]**
Total events	1588		2674			

Heterogeneity: Chi² = 93.53, df = 48 (P < 0.0001); I² = 49%
Test for overall effect: Z = 6.16 (P < 0.00001)

Figure 3 Forest plot of survival rate monotherapy vs combination therapy.

The meta-analysis assessment on survival rates between dual antibiotic combination therapy and multiple combination therapy (more than 2 antibiotic regimens) revealed no significant difference (**Figure 4**). Nonetheless, the meta-analysis indicated a positive trend in survival rates for the double combination group relative to the double combination group (OR = 1.17, 95 % CI (0.95, 1.46), $p = 0.15$, $I^2 = 44$ %). The result exhibited a low degree of heterogeneity ($I^2 = 44$ %), signifying a high level of confidence in the findings [69].



Study or Subgroup	Dual Events	Dual Total	Multiple Events	Multiple Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Brescini, 2019	14	24	47	66	7.0%	0.57 [0.21, 1.49]
Daikos, 2014	53	78	19	22	6.4%	0.33 [0.09, 1.24]
Diaz, 2016	10	17	3	5	1.3%	0.95 [0.12, 7.28]
Falcone, 2016	26	39	40	63	6.8%	1.15 [0.50, 2.66]
Gomez-Simmonds, 2016	53	76	22	40	5.8%	1.89 [0.85, 4.16]
Gorgulho, 2020	26	33	2	2	0.7%	0.71 [0.03, 16.37]
Jaber, 2024	16	28	13	23	4.1%	1.03 [0.34, 3.12]
Ji, 2015	30	40	3	5	0.9%	2.00 [0.29, 13.74]
Kontopidou, 2014	29	37	6	6	1.6%	0.27 [0.01, 5.23]
Li, 2019	19	40	1	3	0.7%	1.81 [0.15, 21.59]
Liao, 2017	44	57	13	15	3.1%	0.52 [0.10, 2.61]
Machuca, 2017	28	40	26	32	5.8%	0.54 [0.18, 1.64]
Nagvekar, 2021	8	11	2	2	0.8%	0.49 [0.02, 12.93]
Oliveira, 2015	20	31	6	9	2.2%	0.91 [0.19, 4.37]
Onal, 2023	16	27	12	35	2.8%	2.79 [0.99, 7.87]
Papadimitriou-Olivgeris, 2021	9	13	60	85	3.3%	0.94 [0.26, 3.33]
Tumbarello, 2012	33	56	19	23	7.4%	0.30 [0.09, 1.01]
Tumbarello, 2015	101	142	156	229	23.1%	1.15 [0.73, 1.82]
Wang, 2018	16	19	0	1	0.1%	14.14 [0.47, 424.67]
Zarkotou, 2010	13	14	6	6	0.6%	0.69 [0.02, 19.43]
Zhang, 2020a	46	71	8	9	3.3%	0.23 [0.03, 1.95]
Zhang, 2020b	248	281	58	86	7.0%	3.63 [2.03, 6.47]
Zhang 2023	29	41	29	48	5.2%	1.58 [0.65, 3.85]
Total (95% CI)		**1215**		**815**	**100.0%**	**1.17 [0.95, 1.46]**
Total events	887		551			

Heterogeneity: Chi² = 38.97, df = 22 (P = 0.01); I² = 44%
Test for overall effect: Z = 1.45 (P = 0.15)

Figure 4 Forest plot of survival rate dual combination therapy vs multiple combination therapy.

To detect potential publication bias and Outcome Variability, a funnel plot analysis was performed. The first funnel plot in **Figure 5(A)** compares the survival rates of monotherapy versus combination therapy, while the second funnel plot in **Figure 5(B)** compares dual combination therapy versus multiple combination therapy. In both plots, the symmetry around the vertical line at OR = 1 suggests no significant publication bias. The concentration of data points at the top of the plots indicates larger sample sizes and more precise estimates. Most data points cluster around the OR = 1 line, indicating no strong evidence favoring 1 therapy over the other in terms of survival rates. Both plots also have a few outliers, which may represent studies with extreme results or potential biases. Overall, the interpretation of both funnel plots is similar, with no significant publication bias and no strong preference for either therapy in terms of survival rates. The main distinction is the specific therapies being compared in each plot.

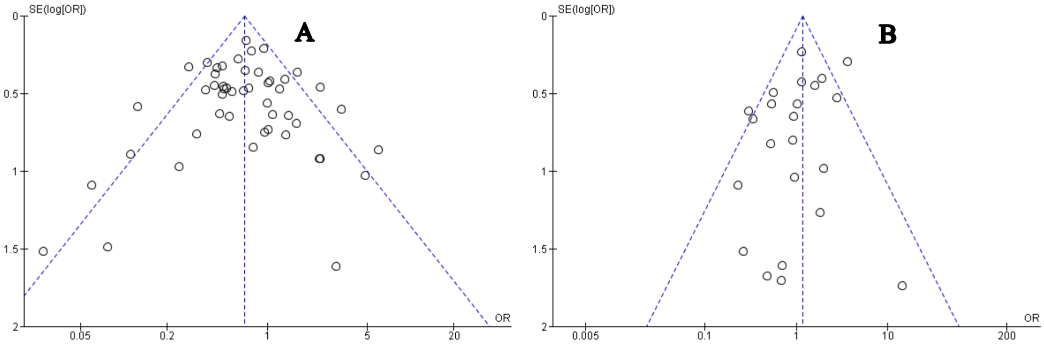
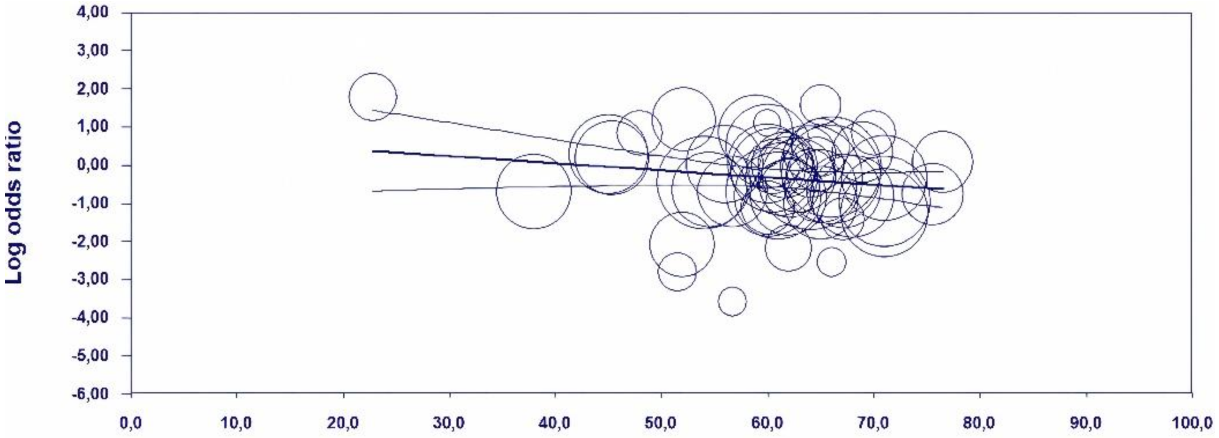


Figure 5 (A) Funnel plot of survival rate monotherapy vs combination therapy; (B) Funnel plot of survival rate dual combination therapy vs multiple combination therapy.

Dual therapy antibiotics are believed to enhance survival rates more effectively than multiple combinations, as fewer and simpler regimens can mitigate the risk of drug toxicity [82]. This may happen because the medicine combination enhances the synergistic benefits of the healing mechanisms while simultaneously posing the danger of synergistic drug toxicity. Research indicates that the cumulative toxicity of many antibiotics may exceed the toxicity of each antibiotic administered individually [82]. The toxicity of antibiotic combinations varies based on the specific antibiotic, dosage, and usage conditions. [83]. This results in considerable variability in effects among people; hence, whereas dual combination antibiotics demonstrate a higher survival rate, the difference relative to multiple combination treatment is not substantial.

One of the factors that can potentially affect the success of therapy is the age of the patient. Studies examining the correlation between age and infection survival rates in hospitalized patients yield inconsistent findings. Therefore, a meta-regression on age was conducted to determine how significant an effect age has on the outcome of mono vs combination therapy. The results of the meta-regression analysis (**Figure 6**) showed that age had no significant influence on the effectiveness of combination therapy versus monotherapy in patients infected with *Enterobacterales*. The regression coefficient for age was −0.0191 with a *p*-value of 0.0826, which showed a negative trend meaning as age increases, the survival rate decreases but was not statistically significant. Simultaneous tests showed that all coefficients, including age, were not significantly different from zero ($p = 0.0826$). Although there was variability between studies ($I^2 = 45.92$ %), the model explained only a small amount of variability ($R^2 = 0.07$), indicating that other factors may play a greater role in influencing the effectiveness of therapy. The regression graph also shows that the relationship between age and log odds ratio tends to be weak and inconsistent.



Coefficient	SE	Z-value	*p*-value	Q	τ^2	R^2
−0.0224	0.0127	−1.77	0.0767	3.13	0.0431	0.35

Figure 6 Meta-regression analysis of the log odds ratio in relation to age.

The dose and ratio of antibiotic combinations significantly determine whether their harmful effects are synergistic or antagonistic [84], therefore the management of drug dosage and adherence to combination antibiotic regimens are critical for controlling drug effects in patients. Administering multiple antibiotic combination therapy (more than 2 antibiotic regimens) is more complex than dual combination therapy, resulting in a higher risk of non-adherence among patients. This elevates the risk of toxicity within the multiple combination group [85], making dual combination therapy safer. In addition, the use of 2 antibiotics is expected to be more cost-effective compared to the use of more than 2 drugs, as it reduces the risk of resistance and increases treatment effectiveness, which can reduce the need for additional care or further treatment [86,87].

Overall, the use of dual combination antibiotics shows the best effect in increasing patient survival rates. However, this study did not compare the effects of antibiotics based on the classification of severity levels and comorbidities, raising concerns about potentially inaccurate comparisons that may not align with the conditions of each patient. This is due to inconsistencies in reporting patient severity at hospital presentation among the inclusion studies. In addition, this study also does not compare the safety rate of both combination types, so further research is needed for a more detailed investigation.

Conclusions

The use of combination antibiotics markedly enhances the survival rate when compared to monotherapy antibiotics. Nonetheless, the use of a dual antibiotic combination yields a superior survival rate in comparison to multiple antibiotics, albeit not to a significant extent. Further studies are recommended to explore the safety and cost-effectiveness of both combination types. Furthermore, it is advisable for subsequent studies to present more comprehensive findings that include classifications of patient severity and comorbidities. Furthermore, conducting a network meta-analysis is essential to provide more precise recommendations regarding which combination therapies exhibit greater potential.

Acknowledgements

The authors thank everyone who contributed to the successful completion of this study. Special thanks are due to Faculty of Medicine, University of Jember, Indonesia for providing the necessary resources and support throughout the research process. We also thank our colleagues and collaborators for their helpful discussions and comments.

References

[1] Y Xu, Y Liu, Y Liu, J Pei, S Yao and C Cheng. Bacteriophage therapy against *Enterobacteriaceae*. *Virologica Sinica* 2015; **30(1)**, 11-18.

[2] LK Logan and RA Weinstein. The epidemiology of Carbapenem-resistant *Enterobacteriaceae*: The impact and evolution of a global menace. *The Journal of Infectious Diseases* 2017; **215(S1)**, S28-S36.

[3] M Shi. Overview of Carbapenem-resistant *Enterobacteriaceae*. *Biomedical Journal of Scientific & Technical Research* 2021; **39(2)**, 31248-31251.

[4] B Tuhamize and J Bazira. Carbapenem-resistant *Enterobacteriaceae* in the livestock, humans and environmental samples around the globe: A systematic review and meta-analysis. *Scientific Reports* 2024; **14(1)**, 16333.

[5] MM Mustafai, M Hafeez, S Munawar, S Basha, AA Rabaan, MA Halwani, A Alawfi, A Alshengeti, MA Najim, S Alwarthan, MK Al-Fonaisan, SA Almuthree, M Garout and N Ahmed. Prevalence of Carbapenemase and extended-spectrum β-lactamase producing *Enterobacteriaceae*: A cross-sectional study. *Antibiotics* 2023; **12(1)**, 1-14.

[6] N Djadjiti, OE Kelechi, OF Nwagbara and S Dane. Prevalence of *Enterobacteriaceae* among children aged 5-15 from some selected hospitals in Abuja, Nigeria. *Journal of Research in Medical and Dental Science* 2020; **8(2)**, 33-38.

[7] M Tilahun, Y Kassa, A Gedefie and M Ashagire. Emerging carbapenem-resistant *Enterobacteriaceae* infection, its epidemiology and novel treatment options: A review. *Infection and Drug Resistance* 2021; **14**, 4363-4374.

[8] CC Sheu, YT Chang, SY Lin, YH Chen and PR Hsueh. Infections caused by Carbapenem-resistant *Enterobacteriaceae*: An update on therapeutic options. *Frontiers in Microbiology* 2019; **10**, 80.

[9] A Martin, K Fahrbach, Q Zhao and T Lodise. Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to *Enterobacteriaceae*: Results of a systematic literature review and meta-analysis. *Open Forum Infectious Diseases* 2018; **5(7)**, ofy150.

[10] R Zhou, X Fang, J Zhang, X Zheng, S Shangguan, S Chen, Y Shen, Z Liu, J Li, R Zhang, J Shen, TR Walsh and Y Wang. Impact of carbapenem resistance on mortality in patients infected with *Enterobacteriaceae*: A systematic review and meta-analysis. *BMJ Open* 2021; **11(12)**, 1-12.

[11] AT Aslan and M Akova. Extended spectrum β-lactamase producing *Enterobacteriaceae*: Carbapenem sparing options. *Expert Review of Anti-infective Therapy* 2019; **17(12)**, 969-981.

[12] J Harting. Carbapenem-resistant *Enterobacteriaceae* infections: A review of epidemiology and treatment options. *The University of Louisville Journal of Respiratory Infections* 2019; **3(1)**, 4.

[13] U Amaldi and S Braccini. Present and future of hadrontherapy. *AIP Conference Proceedings* 2006; **827**, 248-261.

[14] EM Trecarichi and M Tumbarello. Therapeutic options for carbapenem-resistant Enterobacteriaceae infections. *Virulence* 2017; **8(4)**, 470-484.

[15] PI Rafailidis and ME Falagas. Options for treating carbapenem-resistant *Enterobacteriaceae*. *Current Opinion in Infectious Diseases* 2014; **27(6)**, 479-483.

[16] E Mouloudi, E Protonotariou, A Zagorianou, E Iosifidis, A Karapanagiotou and T Giasnetsova. Bloodstream infections caused by metallo- β -lactamase/*Klebsiella pneumoniae* Carbapenemase - producing *K. pneumoniae* among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes. *Infection Control & Hospital Epidemiology* 2010; **31(12)**, 1250-1506.

[17] O Zarkotou, S Pournaras, P Tselioti, V Dragoumanos, V Pitiriga, K Ranellou, A Prekates, K Themeli-Digalaki and A Tsakris. Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment. *Clinical Microbiology and Infection* 2011; **17(12)**, 1798-803.

[18] C Navarro-San Francisco, M Mora-Rillo, MP Romero-Gómez, F Moreno-Ramos, A Rico-Nieto, G Ruiz-Carrascoso, R Gómez-Gil, JR Arribas-López, J Mingorance and JR Paño-Pardo. Bacteraemia due to OXA-48-Carbapenemase-producing *Enterobacteriaceae*: A major clinical challenge. *Clinical Microbiology and Infection* 2013; **19(2)**, E72-E79.

[19] M Tumbarello, P Viale, C Viscoli, EM Trecarichi, F Tumietto, A Marchese, T Spanu, S Ambretti, F Ginocchio, F Cristini, AR Losito, S Tedeschi, R Cauda and M Bassetti. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* Carbapenemase-producing K. pneumoniae: Importance of combination therapy. *Clinical Infectious Diseases* 2012; **55(7)**, 943-950.

[20] F Kontopidou, H Giamarellou, P Katerelos, A Maragos, I Kioumis, E Trikka-Graphakos, C Valakis and HC Maltezou. Infections caused by carbapenem-resistant Klebsiella pneumoniae among patients in intensive care units in Greece: A multicentre study on clinical outcome and therapeutic options. *Clinical Microbiology and Infection* 2014; **20(2)**, O117-O123.

[21] S Ji, F Lv, X Du, Z Wei, Y Fu, X Mu, Y Jiang and Y Yu. Cefepime combined with amoxicillin/clavulanic acid: A new choice for the KPC-producing K. pneumoniae infection. *International Journal of Infectious Diseases* 2015; **38**, 108-114.

[22] M Tumbarello, EM Trecarichi, F Giuseppe De Rosa, M Giannella, DR Giacobbe, M Bassetti, AR Losito, M Bartoletti, VD Bono, S Corcione, G Maiuro, S Tedeschi, L Celani, CS Cardellino, T Spanu, A Marchese, S Ambretti, R Cauda, C Viscoli and P Viale. Infections caused by KPC-producing *Klebsiella pneumoniae*: Differences in therapy and mortality in a multicentre study. *Journal of Antimicrobial Chemotherapy* 2015; **70(7)**, 2133-2143.

[23] M Falcone, A Russo, A Iacovelli, G Restuccia, G Ceccarelli, A Giordano, A Farcomeni, A Morelli and M Venditti. Predictors of outcome in ICU patients with septic shock caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. *Clinical Microbiology and Infection* 2016; **22(5)**, 444-450.

[24] A Gomez-Simmonds, B Nelson, DP Eiras, A Loo, SG Jenkins, S Whittier, DP Calfee, MJ Satlin, CJ Kubin and EY Furuya. Combination regimens for treatment of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. *Antimicrobial Agents and Chemotherapy* 2016; **60(6)**, 3601-3607.

[25] Y Liao, GH Hu, YF Xu, JP Che, M Luo, HM Zhang, B Peng, XD Yao, JH Zheng and M Liu. Retrospective analysis of fosfomycin combinational therapy for sepsis caused by carbapenem-resistant *Klebsiella pneumoniae*. *Experimental and Therapeutic Medicine* 2017; **13(3)**, 1003-1010.

[26] M Papadimitriou-Olivgeris, F Fligou, C Bartzavali, A Zotou, A Spyropoulou and K Koutsileou. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infection in critically ill patients: risk factors and predictors of mortality. *European Journal of Clinical Microbiology & Infectious Diseases* 2017; **36(7)**, 1125-1131.

[27] C Li, Y Li, Z Zhao, Q Liu and B Li. Treatment options and clinical outcomes for carbapenem-resistant Enterobacteriaceae bloodstream infection in a Chinese university hospital. *Journal of Infection and Public Health* 2019; **12(1)**, 26-31.

[28] M Tumbarello, EM Trecarichi, A Corona, FG De Rosa, M Bassetti, C Mussini, F Menichetti, C Viscoli, C Campoli, M Venditti, A De Gasperi, A Mularoni, C Tascini, G Parruti, C Pallotto, S Sica, E Concia, R Cultrera, G De Pascale, …, P Viale. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* Carbapenemase-producing *K. pneumoniae*. *Clinical Infectious Diseases* 2019; **68(3)**, 355-364.

[29] S Zhang, Z Yang, L Sun, Z Wang, L Sun, J Xu, L Zeng and T Sun. Clinical observation and prognostic analysis of patients with *Klebsiella pneumoniae* bloodstream infection. *Frontiers in Cellular and Infection Microbiology* 2020; **10**, 577244.

[30] IR Chen, PH Huang, PF Wu, FD Wang and YT Lin. Clinical characteristics and outcomes of 56 patients with pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae. Journal of Global Antimicrobial Resistance* 2021; **25**, 326-330.

[31] YY Luan, YH Chen, X Li, ZP Zhou, JJ Huang, ZJ Yang, JJ Zhang and M Wu. Clinical characteristics and risk factors for critically Ill patients with Carbapenem-resistant *Klebsiella pneumoniae* (CrKP): A cohort study from developing country. *Infection and Drug Resistance* 2021; **14**, 5555-5562.

[32] MH Rigatto, F Ramos, A Barros, S Pedroso, I Guasso, L Gonçalves, P Bergo and AP Zavascki. Double-, single- and none-carbapenem-containing regimens for the treatment of carbapenem-resistant *Enterobacterales* (CRE) bloodstream infections: A retrospective cohort. *Journal of Antimicrobial Chemotherapy* 2022; **77(11)**, 3118-3125.

[33] G Zheng, J Cai, L Zhang, D Chen, L Wang, Y Qiu, H Deng, H Bai, X Bian and J He. Ceftazidime/avibactam-based versus polymyxin b-based therapeutic regimens for the treatment of Carbapenem-resistant *Klebsiella pneumoniae* infection in critically Ill patients: A retrospective cohort study. *Infectious Diseases and Therapy* 2022; **11(5)**, 1917-1934.

[34] U Önal, NÜ Tüzemen, PK Kaya, R İşçimen, NK Girgin, C Özakın, FŞ Kahveci and H Akalın. Evaluation of the combination treatments with intravenous fosfomycin for carbapenem-resistant *Klebsiella pneumoniae*. *Revista da Associação Médica Brasileira* 2023; **69(11)**, 12-17.

[35] AMR Abu Jaber, B Basgut, AA Hawan, AA Al Shehri, SA AlKahtani, NJ Ahmed and A Abdi. The clinical efficacy of adding ceftazidime/avibactam to standard therapy in treating infections caused by Carbapenem-resistant *Klebsiella pneumonia* with blaOXA-48-like genes. *Antibiotics* 2024; **13(3)**, 265.

[36] J Li, W Wu, M Wu, Z Zhou, J Wang, M Qiu, L Xu, J Ren and X Wu. Clinical and molecular characteristics of patients with bloodstream infections caused by KPC and NDM co-producing carbapenem-resistant *Klebsiella pneumoniae*. *Infection and Drug Resistance* 2024; **17**, 1685-1697.

[37] M Nguyen, GA Eschenauer, M Bryan, K O'Neil, EY Furuya, P Della-Latta and CJ Kubin. Carbapenem-resistant *Klebsiella pneumoniae* bacteremia: Factors correlated with clinical and microbiologic outcomes. *Diagnostic Microbiology and Infectious Disease* 2010; **67(2)**, 180-184.

[38] A Capone, M Giannella, D Fortini, A Giordano, M Meledandri, M Ballardini, M Venditti, E Bordi, D Capozzi, MP Balice, A Tarasi, G Parisi, A Lappa, A Carattoli and N Petrosillo. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. *Clinical Microbiology and Infection* 2013; **19(1)**, E23-E30.

[39] ZA Qureshi, DL Paterson, BA Potoski, MC Kilayko, G Sandovsky, E Sordillo, B Polsky, JM Adams-Haduch and Y Doi. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: Superiority of combination antimicrobial regimens. *Antimicrobial Agents and Chemotherapy* 2012; **56(4)**, 2108-2113.

[40] GL Daikos, S Tsaousi, LS Tzouvelekis, I Anyfantis, M Psichogiou, A Argyropoulou, I Stefanou, V Sypsa, V Miriagou, M Nepka, S Georgiadou, A

Markogiannakis, D Goukos and A Skoutelis. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: Lowering mortality by antibiotic combination schemes and the role of carbapenems. *Antimicrobial Agents and Chemotherapy* 2014; **58(4)**, 2322-2328.

[41] M Gonzalez-Padilla, J Torre-Cisneros, F Rivera-Espinar, A Pontes-Moreno, L López-Cerero, A Pascual, C Natera, M Rodríguez, I Salcedo, F Rodríguez-López, A Rivero and J Rodríguez-Baño. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*. *Journal of Antimicrobial Chemotherapy* 2015; **70(3)**, 905-913.

[42] MS De Oliveira, DB De Assis, MP Freire, GVB do Prado, AS Machado, E Abdala, LC Pierrotti, C Mangini, L Campos, HHC Filho and AS Levin. Treatment of KPC-producing *Enterobacteriaceae*: Suboptimal efficacy of polymyxins. *Clinical Microbiology and Infection* 2015; **21(2)**, 179.e1-179.e7.

[43] A Díaz, DC Ortiz, M Trujillo, C Garcés, F Jaimes and AV Restrepo. Clinical characteristics of carbapenem-resistant *Klebsiella pneumoniae* infections in ill and colonized children in Colombia. *The Pediatric Infectious Disease Journal* 2016; **35(3)**, 237-241.

[44] A Ghafur, V Devarajan, T Raja, J Easow, MA Raja, S Sreenivas, B Ramakrishnan, SG Raman, D Devaprasad, B Venkatachalam and R Nimmagadda. Monotherapy versus combination therapy against carbapenem-resistant Gram-negative bacteria: A retrospective observational study. *Indian Journal of Cancer* 2016; **53(4)**, 592-594.

[45] B Gutiérrez-Gutiérrez, E Salamanca, M de Cueto, PR Hsueh, P Viale, JR Paño-Pardo, M Venditti, M Tumbarello, G Daikos, R Cantón, Y Doi, FF Tuon, I Karaiskos, E Pérez-Nadales, MJ Schwaber, ÖK Azap, M Souli, E Roilides, S Pournaras, …, J Rodríguez-Baño. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* (INCREMENT): A retrospective cohort study. *The Lancet Infectious Diseases* 2017; **17(7)**, 726-734.

[46] I Machuca, B Gutiérrez-Gutiérrez, I Gracia-Ahufinger, FR Espinar, Á Cano, J Guzmán-Puche, E Pérez-Nadales, C Natera, M Rodríguez, R León, JJ Castón, F Rodríguez-López, J Rodríguez-Baño and J Torre-Cisneros. Mortality associated with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance: importance of combination therapy without colistin and carbapenems. *Antimicrobial Agents and Chemotherapy* 2017; **61(8)**, e00406-17.

[47] A Sousa, MT Pérez-Rodríguez, A Soto, L Rodríguez, A Pérez-Landeiro, L Martínez-Lamas, A Nodar and M Crespo. Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing *Enterobacteriaceae*. *Journal of Antimicrobial Chemotherapy* 2018; **73(11)**, 3170-3175.

[48] X Wang, Q Wang, B Cao, S Sun, Y Zhang, B Gu, B Li, K Liao, F Zhao, L Jin, C Jin, C Yang, F Pei, Z Zhang and H Wang. Retrospective observational study from a Chinese network of the impact of combination therapy versus monotherapy on. *Antimicrobial Agents and Chemotherapy* 2018; **63(1)**, e01511-e01518.

[49] L Brescini, G Morroni, C Valeriani, S Castelletti, M Mingoia, S Simoni, A Masucci, R Montalti, M Vivarelli, A Giacometti and F Barchiesi. Clinical and epidemiological characteristics of KPC-producing *Klebsiella pneumoniae* from bloodstream infections in a tertiary referral center in Italy. *BMC Infectious Diseases* 2019; **19(1)**, 1-9.

[50] U Önal, OR Sipahi, H Pullukçu, T Yamazhan, B Arda, S Ulusoy, Ş Aydemir and MI Taşbakan. Retrospective evaluation of the patients with urinary tract infections due to carbapenemase producing *Enterobacteriaceae*. *Journal of Chemotherapy* 2019; **32(1)**, 15-20.

[51] A Gorgulho, AM Grilo, M de Figueiredo and J Selada. Carbapenemase- producing enterobacteriaceae in a portuguese hospital - a 5-year retrospective study. *Germs* 2020; **10(2)**, 95-103.

[52] SCJ Jorgensen, TD Trinh, EJ Zasowski, AM Lagnf, S Bhatia, SM Melvin, SP Simon, JR Rosenberg, ME Steed, SJ Estrada, T Morrisette, SL Davis and MJ Rybak. Evaluation of the INCREMENT-CPE, Pitt bacteremia and qPitt scores in

patients with carbapenem-resistant *Enterobacteriaceae* infections treated with ceftazidime - avibactam. *Infectious Diseases and Therapy* 2020; **9(2)**, 291-304.

[53] NY Lee, CS Tsai, LS Syue, PL Chen, CW Li, MC Li and WC Ko. Treatment outcome of bacteremia due to non-carbapenemase producing carbapenem-resistant *Klebsiella pneumoniae* bacteremia: Role of carbapenem combination therapy. *Clinical Therapeutics* 2020; **42(3)**, e33-e44.

[54] G Zhang, M Zhang, F Sun, J Zhou, Y Wang, D Zhu, Z Chen, Q Chen, Q Chang, H Liu, W Chai and H Pan. Epidemiology, mortality and risk factors for patients with *K. pneumoniae* bloodstream infections: Clinical impact of carbapenem resistance in a tertiary university teaching hospital of Beijing. *Journal of Infection and Public Health* 2020; **13(11)**, 1710-1714.

[55] E Eren, A Ulu-Kılıç, Z Türe, F Cevahir, H Kılıç and E Alp-Meşe. Risk factors of mortality in patients with bloodstream infections due to carbapenem resistant *Klebsiella pneumonia*. *Klimik Dergisi* 2021; **34(1)**, 56-60.

[56] V Nagvekar, A Shah, VP Unadkat, A Chavan, R Kohli, S Hodgar, A Ashpalia, N Patil and R Kamble. Clinical outcome of patients on ceftazidime-avibactam and combination therapy in carbapenem-resistant *Enterobacteriaceae*. *Indian Journal of Critical Care Medicine* 2021; **25(7)**, 780-784.

[57] M Papadimitriou-Olivgeris, C Bartzavali, A Georgakopoulou, F Kolonitsiou, C Papamichail, I Spiliopoulou, M Christofidou, F Fligou and M Marangos. Mortality of pandrug-resistant *Klebsiella pneumoniae* bloodstream infections in critically ill patients: A retrospective cohort of 115 episodes. *Antibiotics* 2021; **10(1)**, 76.

[58] WC Tsai, LS Syue, WC Ko, CL Lo and NY Lee. Antimicrobial treatment of monomicrobial phenotypic carbapenem-resistant *Klebsiella pneumoniae* bacteremia: Two are better than one. *Journal of Microbiology, Immunology and Infection* 2021; **55(6)**, 1219-1228.

[59] M Tumbarello, F Raffaelli, M Giannella, E Mantengoli, A Mularoni, M Venditti, FG De Rosa, L Sarmati, M Bassetti, G Brindicci, M Rossi, R Luzzati, PA Grossi, A Corona, A Capone, M Falcone, C Mussini, EM Trecarichi, A Cascio, …, P Viale. Ceftazidime-avibactam use for *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* infections: A retrospective observational multicenter study. *Clinical Infectious Diseases* 2021; **73(9)**, 1664-1676.

[60] AT Aslan, E Kırbaş, B Sancak, ES Tanrıverdi, B Otlu, NC Gürsoy, YA Yılmaz, A Tozluyurt, Ü Liste, A Bıçakcıgil, G Hazırolan, O Dağ, GS Güven and M Akova. A retrospective observational cohort study of the clinical epidemiology of bloodstream infections due to carbapenem-resistant *Klebsiella pneumoniae* in an OXA-48 endemic setting. *International Journal of Antimicrobial Agents* 2022; **59(4)**, 106554.

[61] J Chen, H Ma, X Huang, Y Cui, W Peng, F Zhu, S Ma, M Rao, P Zhang, H Yang, L Su, R Niu and P Pan. Risk factors and mortality of carbapenem-resistant Klebsiella pneumoniae bloodstream infection in a tertiary-care hospital in China: An 8-year retrospective study. *Antimicrobial Resistance & Infection Control* 2022; **11(1)**, 161.

[62] CL Luterbach, H Qiu, PO Hanafin, R Sharma, J Piscitelli, FC Lin, J Ilomaki, E Cober, RA Salata, RC Kalayjian, RR Watkins, Y Doi, CB Landersdorfer, D van Duin and GG Rao. A systems-based analysis of mono- and combination therapy for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. *Antimicrobial Resistance & Infection Control* 2022; **66(10)**, e00591-22.

[63] M Tumbarello, F Raffaelli, A Cascio, M Falcone, L Signorini, C Mussini, FG De Rosa, AR Losito, G De Pascale, R Pascale, DR Giacobbe, A Oliva, A Farese, P Morelli, G Tiseo, M Meschiari, PD Giacomo, F Montagnani and M Fabbiani. Compassionate use of meropenem/vaborbactam for infections caused by KPC-producing *Klebsiella pneumoniae*: A multicentre study. *JAC-Antimicrobial Resistance* 2022; **4(1)**, dlac022.

[64] J Cheng, D Zhao, X Ma and J Li. Molecular epidemiology, risk factors, and outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection in a tertiary hospital in eastern China: For a retrospective study conducted over 4 years. *Frontiers in Microbiology* 2023; **14**, 1223138.

[65] L Zhang, S Zhen, Y Shen, T Zhang, J Wang, J Li, Q Lin, Z Xiao, Y Zheng, E Jiang, M Han and S

Feng. Bloodstream infections due to carbapenem-resistant *Enterobacteriaceae* in hematological patients: Assessment of risk factors for mortality and treatment options. *Annals of Clinical Microbiology and Antimicrobials* 2023; **22(1)**, 41.

[66] Katip, A Rayanakorn, P Oberdorfer, P Taruangsri, T Nampuan and S Okonogi. Comparative effectiveness and mortality of colistin monotherapy versus colistin-fosfomycin combination therapy for the treatment of carbapenem-resistant *Enterobacteriaceae* (CRE) infections: A propensity score analysis. *Journal of Infection and Public Health* 2024; **17(5)**, 727-734.

[67] Y Leibovici-Weissman, N Tau and D Yahav. Bloodstream infections in the elderly: What is the real goal? *Aging Clinical and Experimental Research* 2021; **33(4)**, 1101-1112.

[68] YC Chen, IT Tsai, CH Lai, KH Lin and YC Hsu. Risk factors and outcomes of community-acquired carbapenem-resistant *Klebsiella pneumoniae* infection in elderly patients. *Antibiotics* 2024; **13(3)**, 282.

[69] WG Melsen, MCJ Bootsma, MM Rovers and MJM Bonten. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clinical Microbiology and Infection* 2014; **20(2)**, 123-129.

[70] N Petrosillo, E Ioannidou and ME Falagas. Colistin monotherapy vs. combination therapy: Evidence from microbiological, animal and clinical studies. *Clinical Microbiology and Infection* 2008; **14(9)**, 816-827.

[71] A Schmid, A Wolfensberger, J Nemeth, PW Schreiber, H Sax and SP Kuster. Monotherapy versus combination therapy for multidrug-resistant Gram-negative infections: Systematic review and meta-analysis. *Scientific Reports* 2019; **9(1)**, 15290.

[72] P Poulikakos, GS Tansarli and ME Falagas. Combination antibiotic treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant Acinetobacter infections: A systematic review. *European Journal of Clinical Microbiology and Infectious Diseases* 2014; **33**, 1675-1685.

[73] GJ Sullivan, NN Delgado, R Maharjan and AK Cain. How antibiotics work together: Molecular mechanisms behind combination therapy. *Current Opinion in Microbiology* 2020; **57**, 31-40.

[74] Z Gounani, MA Asadollahi, JN Pedersen, J Lyngsø, JS Pedersen, A Arpanaei and RL Meyer. Mesoporous silica nanoparticles carrying multiple antibiotics provide enhanced synergistic effect and improved biocompatibility. *Colloids Surfaces B Biointerfaces* 2019; **175**, 498-508.

[75] I Baltas, T Stockdale, M Tausan, A Kashif, J Anwar, J Anvar, E Koutoumanou, D Sidebottom, V Garcia-Arias, M Wright and J Democratis. Impact of antibiotic timing on mortality from Gram-negative bacteraemia in an English district general hospital: The importance of getting it right every time. *Journal of Antimicrobial Chemotherapy* 2021; **76(3)**, 813-819.

[76] YF Zhou, P Liu, CJ Zhang, XP Liao, J Sun and YH Liu. Colistin combined with tigecycline: A promising alternative strategy to combat *Escherichia coli* harboring blaNDM-5 and mcr-1. *Frontiers in Microbiology* 2020; **10**, 2957.

[77] X Cai, Z Yang, J Dai, K Chen, L Zhang, W Ni, C Wei and J Cui. Pharmacodynamics of tigecycline alone and in combination with colistin against clinical isolates of multidrug-resistant Acinetobacter baumannii in an *in vitro* pharmacodynamic model. *International Journal of Antimicrobial Agents* 2017; **49(5)**, 609-616.

[78] S Fergadaki, G Renieris, N Machairas, L Sabracos, DI Droggiti, E Misiakos and EJ Giamarellos-Bourboulis. Efficacy of tigecycline alone or in combination for experimental infections by KPC carbapenemase-producing *Klebsiella pneumoniae*. *International Journal of Antimicrobial Agents* 2021; **58(3)**, 106384.

[79] AA Agyeman, PJ Bergen, GG Rao, RL Nation and CB Landersdorfer. A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* infections. *International Journal of Antimicrobial Agents* 2020; **55(1)**, 105833.

[80] J Wang, Y Pan, J Shen and Y Xu. The efficacy and safety of tigecycline for the treatment of bloodstream infections: A systematic review and meta-analysis. *Annals of Clinical Microbiology and Antimicrobials* 2017; **16**, 1-10.

[81] IL Cheng, YH Chen, CC Lai and HJ Tang. Intravenous colistin monotherapy versus combination therapy against carbapenem-resistant gram-negative bacteria infections: Meta-analysis of randomized controlled trials. *Journal of Clinical Medicine* 2018; **7(8)**, 208.

[82] Y Luan, K Chen, J Zhao and L Cheng. Comparative study on synergistic toxicity of enrofloxacin combined with three antibiotics on proliferation of THLE-2 cell. *Antibiotics* 2022; **11(3)**, 394.

[83] F Shahbazi, L Shojaei, F Farvadi and S Kadivarian. Antimicrobial safety considerations in critically ill patients: Part II: Focused on anti-microbial toxicities. *Expert Review of Clinical Pharmacology* 2022; **15(5)**, 563-573.

[84] Y Wang, C Gao, Z Qu and M Li. The combined toxicity of binary mixtures of antibiotics against the cyanobacterium Microcystis is dose-dependent: Insight from a theoretical nonlinear combined toxicity assessment method. *Environmental Science and Pollution Research* 2022; **29(8)**, 1-13.

[85] S Bangalore, G Kamalakkannan, S Parkar and FH Messerli. Fixed-dose combinations improve medication compliance: A meta-analysis. *American Journal of Medicine* 2007; **120(8)**, 713-719.

[86] B Tepekule, H Uecker, I Derungs, A Frenoy and S Bonhoeffer. Modeling antibiotic treatment in hospitals: A systematic approach shows benefits of combination therapy over cycling, mixing, and mono-drug therapies. *PLoS Computational Biology* 2017; **13(9)**, e1005745.

[87] C Nyhoegen, S Bonhoeffer and H Uecker. The many dimensions of combination therapy: How to combine antibiotics to limit resistance evolution. *Evolutionary Applications* 2024; **17(8)**, 1-25.

Supplementary Materials

Table S1 Search strategies.

Database	Keywords	Total articles
PubMed	#1 Enterobacteriaceae[Mesh Terms] #2 ("Enterobacteriaceae" OR "Escherichia coli" OR "Proteus mirabilis" OR Enterobacter OR "Serratia" OR "Citrobacter" OR "Klebsiella" OR "Salmonella" OR "Shigella") #3 #1 OR #2 #4 β-lactamase[Mesh Terms] #5 (“β-lactamase” OR “ESBL” OR “beta lactamase”) #6 #4 OR #5 #7 Antibiotic[Mesh Terms] #8 (Antibiotic OR Antimicrobial OR Antibacteria) #9 #7 OR #8 #10 (Combination OR Combined OR mono) #11 (Survive OR Survival OR Died OR mortality OR death) #12 #3 AND #6 AND #9 AND #10 AND #11	350
Cochrane Library	#1 Enterobacteriaceae[Mesh Terms] #2 ("Enterobacteriaceae" OR "Escherichia coli" OR "Proteus mirabilis" OR Enterobacter OR "Serratia" OR "Citrobacter" OR "Klebsiella" OR "Salmonella" OR "Shigella") #3 #1 OR #2 #4 β-lactamase[Mesh Terms] #5 (“β-lactamase” OR “ESBL” OR “beta lactamase”) #6 #4 OR #5 #7 Antibiotic[Mesh Terms] #8 (Antibiotic OR Antimicrobial OR Antibacteria) #9 #7 OR #8 #10 (Combination OR Combined OR mono) #11 (Survive OR Survival OR Died OR mortality OR death) #12 #3 AND #6 AND #9 AND #10 AND #11 #13 (Cohort OR Case control OR Retrospective OR Observational) #14 #12 AND #13	7
SCOPUS	("Enterobacteriaceae" OR "Escherichia" OR "Proteus" OR Enterobacter OR "Serratia" OR "Citrobacter" OR "Klebsiella" OR "Salmonella" OR "Shigella") AND (“β-lactamase” OR “ESBL” OR “beta lactamase”) AND ("Monotherapy" OR "Mono" OR "Combination") AND ("Antibiotic") AND ("Cohort" OR "Case control" OR "Retrospective" OR "Observational") AND (Survive OR Survival OR Died OR mortality OR death)	380
EBSCOhost	("Enterobacteriaceae" OR "Escherichia" OR "Proteus" OR Enterobacter OR "Serratia" OR "Citrobacter" OR "Klebsiella" OR "Salmonella" OR "Shigella") AND (“β-lactamase” OR “ESBL” OR “beta lactamase”) AND ("Monotherapy" OR "Mono" OR "Combination") AND ("Antibiotic") AND ("Cohort" OR "Case control" OR "Retrospective" OR "Observational") AND (Survive OR Survival OR Died OR mortality OR death)	47
ScienceDirect	("Enterobacteriaceae") AND (“β-lactamase”) AND ("Monotherapy" OR "Combination") AND ("Antibiotic") AND ("Observational") AND (Survival OR mortality)	239

Table S2 Extraction table.

No.	Study	N	Age, Mean (SD)/Median [*range/IQR*]	Regimens	Type of infection	Type of bacteria	Observation length
1	Mouloudi *et al.* [16]	59	45 [15-78]	**Mono:** CTN **Dual:** CTN+GTC	Bloodstream	*Klebsiella pneumoniae*	N/A
2	Nguyen *et al.* [37]	48	60 [37-86]	**Mono:** PMB, TGC **Dual:** PMB+TGC	Bloodstream	*Klebsiella pneumoniae*	30 days
3	Zarkotou *et al.* [17]	53	56.7 (20.9)	**Mono:** CTN, TGC, GTC, CBM **Dual:** TGC+CTN, TGC+GTC, TGC+CBM, TGC+AMC **Multiple:** TGC+CTN+CBM, TGC+CTN+GTC, TGC+CBM+GTC	Bloodstream	*Klebsiella pneumoniae*	14 days
4	Capone *et al.* [38]	91	69 [50-77]	**Mono:** GTC, CTN **Dual:** CTN+TGC, CTN+FMC, CTN+GTC, TGC+FMC	Lung, Bloodstream, Urinary tract, Skin and soft tissue, intra-abdominal	*Klebsiella pneumoniae*	N/A
5	Francisco *et al.* [18]	40	70 [38-92]	**Mono:** CTN, TGC, AMC, CBM **Combination:** Not elaborated	Urinary tract, intra-abdominal, bloodstream, others	*Klebsiella pneumoniae, Escherichia coli*	30 days
6	Qureshi *et al.* [39]	41	62 [25-90]	**Mono:** TGC, CBM, GTC, BL/BLI, CLX **Dual:** TGC+CBM, TGC+AGS, CBM+FQL, AZT+FQL, CFM+GTC, CLX+CBM, CLX+TGC, CLX+FQL	Bloodstream	*Klebsiella pneumoniae*	28 days
7	Tumbarello *et al.* [19]	125	68 [55 -76]	**Mono:** TGC, CTN, GTC **Dual:** TGC+CTN, TGC+GTC Others **Multiple:** TGC+CTN+MRM, Others	Bloodstream	*Klebsiella pneumoniae*	30 days
8	Daikos *et al.* [40]	205	60.2 (18.9)	**Mono:** TGC, CTN, AGS, CBM, Others **Dual:** CBM+TGC, CBM+AGS, CBM+CTN, TGC+AGS, TGC+CTN, AGS+CTN **Multiple:** CBM+TGC+AGS/CTN, TGC+AGS+CTN.	Bloodstream	*Klebsiella pneumoniae*	28 days
9	Kontopidou *et al.* [20]	127	61.3 [17-86]	**Mono:** CTN, AGS, TGC, QNL **Dual:** TGC+AGS, CTN+AGS, CTN+TGC **Multiple:** CTN+TGC+AGS, CTN+TGC+CBM	Lung, bloodstream, urinary tract, skin and soft tissue, intra-abdominal	*Klebsiella pneumoniae*	14 days

No.	Study	N	Age, Mean (SD)/Median [*range/IQR*]	Regimens	Type of infection	Type of bacteria	Observation length
10	Gonzalez-Padilla *et al.* [41]	50	60.5 [19-86]	**Mono:** TGC, GTC, MRM **Dual:** TGC+GTC, MRM+FMC, TGC+CTN **Multiple:** MRM+CTN+FMC	Lung, urinary tract, intra-abdominal, skin and soft tissue, bloodstream, nervous system, luka operasi, endocardium	*Klebsiella pneumoniae*	30 days
11	Ji *et al.* [21]	51	67.1 (16.1)	**Mono:** TGC **Dual:** TGC+FMC, TGC+CFM, TGC+MRM, CFM+ BL/BLI **Multiple:** CFM+BL/BLI+ FMC, TGC+AMC+LVX	Lung, intra-abdominal, bloodstream, urinary tract, others	*Klebsiella pneumoniae*	28 days
12	Oliveira *et al.* [42]	118	56 [1-87]	**Mono**: CBM, PMN, AGS, TGC **Dual**: PMN+CBM, AGS+CBM. AGS+TGC, TGC+CBM, PMN+AGS **Multiple**: PMN+AGS+CBM, TGC+CBM+PMN, AGS+PMN+TGC, AGS+CBM+TGC	Bloodstream, lungs, urinary tract, surgical site infection, Intra-abdominal	*Klebsiella pneumoniae*	30 days
13	Tumbarello *et al.* [22]	661	64 [51-75]	**Mono:** TGC, CTN, GTC **Dual:** Not elaborated **Multiple:** Not elaborated	Bloodstream, lung, intra-abdominal, urinary tract, others	*Klebsiella pneumoniae*	14 days
14	Díaz *et al.* [43]	89	22.8 [0-156]	**Mono:** CTN, AGS, CPF **Dual:** MRM+CTN, MRM+CPF, CTN+AGS, CTN+TGC, CTN+CPF, CFM+AZT, CFM+AGS, CPF+AGS, TGC+AGS **Multiple:** CTN+AGS+TGC, CTN+CPF+AGS	Urinary tract, Intra-abdominal, lung, skin and soft tissue, bloodstream, others	*Klebsiella pneumoniae*	N/A
15	Falcone *et al.* [23]	111	59 (15.2)	**Dual:** MRM+CTN, CTN+TGC, TGC+GTC, MRM+TGC **Multiple:** CTN+TGC+MRM, TGC+MRM+FMC, CTN+TGC+IMP, CTN+TGC+RIF, CRM+ETP+CTN, CTN+TGC+MRM+GTC	Bloodstream, lung, urinary tract, intra-abdominal, others	*Klebsiella pneumoniae*	30 days
16	Ghafur *et al.* [44]	91	45.4 (16.3)	**Mono:** CTN **Dual:**	Bloodstream	*Klebsiella pneumoniae,*	28 days

No.	Study	N	Age, Mean (SD)/Median [*range/IQR*]	Regimens	Type of infection	Type of bacteria	Observation length
				CTN+TGC CTN+MRM		*Acinetobacter baumannii, Escheria coli, Pseudomonas*	
17	Gomez-Simmonds *et al.* [24]	36	60 [47-74]	**Mono:** PMB, TGC, AGS **Dual:** PMB+BL, TGC+BL, BL+AGS, Other+BL TGC+AGS, PMB+TGC, PMB+AGS **Multiple:** PMB+AGS+BL, PMB+TGC+BL, TGC+AGS+BL, PMB+TGC+AGS+BL, PMB+TGC+AGS	Lung, intra-abdominal, mukosa, soft tissue, urinary tract, mix	*Klebsiella pneumoniae*	30 days
18	Gutiérrez-Gutiérrez *et al.* [45]	437	66 [55.5-76]	**Mono:** CTN, CBM, BL, TGC, AGS, Others **Combination:** TGC/CTN/ AGS/CBM/ FMC/Others based therapy	Bloodstream, lung, intra-abdominal, skin, others	*Klebsiella pneumoniae*	30 days
19	Liao *et al.* [25]	107	67.2 (15.7)	**Mono:** BL/BLI, AGS, CEF, QNL, CBM, TGC, MNC **Dual:** FMC+MRM, TGC+MRM, TGC+MNC, MNC+CBM, MNC+BL/BLI, GTC+MRM, AMC+MRM, AMC+CFM, AMC+BL/BLI, CFM+BL/BLI, CFM+STX, CFM+AZT, BL/BLI+ QNL, CBM+QNL, BL/BLI+CBM **Multiple:** FMC+MRM+TTC, TGC+MRM+AMC, TGC+MNC+MRM	Bloodstream, lung, urinary tract, intra-abdominal	*Klebsiella pneumoniae*	45 days
20	Machuca *et al.* [46]	72	62 [74.25-47]	**Mono:** TGC, GTC, FMC **Dual:** TGC+GTC, TGC+FMC, GTC+FMC, **Multiple:** TGC+FMC+GTC	Bloodstream, urinary tract, lung	*Klebsiella pneumoniae*	30 days
21	Papadimitriou-Olivgeris *et al.* [26]	95	56.7 (18.0)	Not elaborated	Bloodstream, abdominal, skin and soft tissue, lungs, urinary tract	*Klebsiella pneumoniae*	30 days
22	Sousa *et al.* [47]	57	64 [26-86]	**Mono:** CAZ/AVI **Multiple:** CTN+TGC+ AMC+IMP	Intra-abdominal, lungs, urinary tract	*Klebsiella pneumoniae.*	30 days
23	Wang *et al.* [48]	98	52.0 [34.3-73]	**Mono:** TGC, CBM, AGS, QNL, STX **Dual:** TGC+AGS, TGC+CBM, TGC+PMB, TGC+STX, CBM+QNL, AGS+QNL,	Abdominal, skin and soft tissue, lungs, catheter	*Klebsiella pneumoniae, Escherichia coli, Enterobacter spp.,*	14 days

No.	Study	N	Age, Mean (SD)/Median [*range/IQR*]	Regimens	Type of infection	Type of bacteria	Observation length
				AGS+CEF, BLI+CEF, BLI+AZT, BLI+MNC, BLI+QNL **Multiple:** AGS+CAZ/AVI+CEF	related, urinary tract	*Citrobacter freundii, and Serratia marcescens.*	
24	Brescini *et al.* [49]	112	65 [54-75]	**Mono:** TGC, CTN, GTC **Multiple:** *Not elaborated*	Lung, intra-abdominal, urinary tract, wounds, others	*Klebsiella pneumoniae*	30 days
25	Li *et al.* [27]	98	47.93 (27.5)	**Mono:** CTN, CFM, MXF, LTX **Dual:** CBM+AMC, CBM+TGC, TGC+AMC, TGC+QNL, AMC+QNL, TGC+CTN, AMC+Other, QNL+Other, TGC+Other **Multiple:** CBM+TGC+QNL, CBM+TGC+AMC	Bloodstream	*Klebsiella pneumoniae, Klebsiella oxytoca, Enterobacter cloacae, Escheria coli, Citrobacter freundii*	30 days
26	Önal *et al.* [50]	100	61.69 (1.65)	**Mono:** CTN, TGC, CBM **Dual:** 2 CBM, CTN+CBM, CTN+TGC, TGC+GTC **Multiple:** contains CTN, CBM, TGC	Urinary tract	*Klebsiella pneumoniae*	30 days
27	Tumbarello *et al.* [28]	104	61 [27-79]	**Mono:** CTN, CAZ/AVI **Dual:** CTN+TGC, 2 CBM, FMC+TGC, CTN+MRM, GTC+TGC, CAZ/AVI+GTC, CAZ/AVI+CTN, CAZ/AVI+CBM, CAZ/AVI+TGC, CAZ/AVI+FMC, CAZ/AVI+AMC **Multiple:** CTN+TGC+MRM	Bloodstream, urinary tract, lungs, abdominal, others	*Klebsiella pneumoniae*	30 days
28	Gorgulho *et al.* [51]	54	75.6 [0-100]	**Mono:** MRM, CTN, CIPRO, CAZ/AVI, Others **Dual:** MRM+AMC, MRM+CTN, TGC+CTN, AMC+CTN, MRM+GTC, MRM+CAZ, CAZ+LZD, CTN+AMP, CTN+TGC, CTN+GTC, GTC+CFM **Multiple:** TGC+PPC/TZB+CLIN, AMC+CTN+CAZ/AVI,	Abdominal, heart disease, skin, others	*K. pneumoniae, Enterobacter cloacae, E. coli, Citrobacter freundii,*	30 days
29	Jorgensen *et al.* [52]	109	63 [53-74]	**Mono:** CAZ/AVI, AMC, PMN, TGC **Combination:** CAZ/AVI combined with others	Lungs, intra-abdominal, urinary tract, skin and soft tissue, osteoarticular, others	*K. pneumoniae, Enterobacter spp, E. coli, K. oxytoca, Citrobacter spp, Serratia, Proteus mirabilis*	30 days
30	Lee *et al.* [53]	171	71 (60-82)	**Mono:** MRM, CTN, CFM **Dual:** CBM+CTN, CBM+AMC, MRM+CPF, CTN+CPF, CTN+AMC, CFM+AMC, PPC+AMC.	Lungs, intra-abdominal, urinary tract, skin and soft tissue	*Klebsiella pneumoniae*	30 days
31	Zhang *et al.* [29]	297	54 (16)	**Mono:** CBM, BL/BLI, CAZ, CFM, CMX **Dual:** TGC+CBM, TGC+PMB, TGC+BL/BLI, TGC+AGS, CBM+PMB, CBM+BL/BLI, CBM+CAZ, BL/BLI+AGS,	Bloodstream	*Klebsiella pneumoniae*	28 days

No.	Study	N	Age, Mean (SD)/Median [*range/IQR*]	Regimens	Type of infection	Type of bacteria	Observation length
				CBM+AGS **Multiple:** TGC+CBM+BL/BLI, TGC+CBM+AGS, TGC+CBM+PMB			
32	Zhang *et al.* [54]	281	65 [46-75]	**Mono:** CBM **Dual:** CBM+TGC **Multiple:** CBM+TGC+others	Bloodstream	*Klebsiella pneumoniae*	28 days
33	Chen *et al.* [30]	56	76.5 [63.8-85]	**Mono:** TGC, CTN **Dual:** TGC+CTN **Multiple:** Others	Not elaborated	*Klebsiella pneumoniae*	14 days
34	Eren *et al.* [55]	82	54.5 [16-88]	**Mono:** TGC, CTN, BL/BLI **Dual:** TGC+CTN, CTN+CBM, CTN+CFM, CTN+ BL/BLI	Bloodstream, lung, urinary tract, others	*Klebsiella pneumoniae*	28 days
35	Luan *et al.* [31]	89	64.0 [48-77]	**Mono:** TGC **Dual:** TGC+FMC, CBM+CBM, QNL+BL/BLI, AMC+Other, CBM+AMC, QNL+CBM, CBM+BL/BLI, FMC+CBM, TGC+CBM, PMB+FMC, QNL+AMC **Multiple:** TGC+FMC+GTC	Bloodstream, lung, intra-abdomen, nervous system, urinary tract, skin and soft tissue, mix	*Klebsiella pneumoniae*	28 days
36	Nagvekar *et al.* [56]	57	60	**Mono:**CAZ/AVI **Dual:** CAZ/AVI+PMN, CAZ/AVI+TCN **Multiple:** CAZ/AVI+PMN+FMC	Intra-abdominal, lungs, urinary tract, bloodstream, others	*Klebsiella pneumoniae, E. coli*	30 days
37	Papadimitriou-Olivgeris *et al.* [57]	115	51.5 (18.6)	**Mono:** CBM, CTN, GTC **Dual:** CBM+AMG, CTN+TGC, CBM+TGC, CBM+TCN **Multiple:** CTN+TGC+AMC, CBM+TGC+AMC, CTN+TGC+CBM, CTN+CBM+AMC+, CTN+TGC+CAZ/AVI, CTN+TGC+FMC, CBM+CTN+TGC+AMC, CBM+CTN+TGC+AMC+Others,	Abdominal, lungs, urinary tract, meningitis, others	*Klebsiella pneumoniae*	N/A
38	Tsai *et al.* [58]	203	71 [60.8-78.3]	**Mono:** CTN, TGC, CBM **Dual:** CBM+CTN, CBM+TGC, CBM+AMC, CTN+TGC	Bloodstream, urinary tract, lung, intra-abdominal, skin and soft tissue	*Klebsiella pneumoniae*	30 days
39	Tumbarello *et al.* [59]	577	66 [56-76]	**Mono:** CAZ/AVI **Dual:** CAZ/AVI+FMC, CAZ/AVI+TGC, CAZ/AVI+GTC, CAZ/AVI+MRM, CAZ/AVI+CTN, CAZ/AVI+AMC, CAZ/AVI+Others **Multiple:** Not elaborated	Bloodstream, urinary tract, lung, intra-abdominal, others	*Klebsiella pneumoniae*	30 days
40	Aslan *et al.* [60]	124	62.1	**Mono:** CBM, CTN, CPF, Others	Bloodstream	*Klebsiella pneumoniae*	30 days

No.	Study	N	Age, Mean (SD)/Median [*range/IQR*]	Regimens	Type of infection	Type of bacteria	Observation length
			(18.0)	**Dual:** MRM+CTN, CTN+TGC, MRM+AGS, Others			
41	Chen *et al.* [61]	212	58.9 (16.0)	Not elaborated	Bloodstream, lungs, intra-abdominal, urinary tract, skin, cerebrospinal fluid	*Klebsiella pneumoniae*	28 days
42	Luterbach *et al.* [62]	49	66 [51-75]	Mono: TGC CTN, CAZ/AVI Dual: CTN+CAZ/AVI	Bloodstream	*Klebsiella pneumoniae*	30 days
43	Rigatto *et al.* [32]	279	60.5 (16.1)	**Mono:** PMB AMC, TGC, CBM **Dual:** CBM+PMB, CBM+ AMC, CBM+TGC **Multiple:** 2 CBM+PMB, 2 CBM+AMC, 2 CAR+TGC	Lungs, abdominal, urinary tract, skin and soft tissue, catheter, others	*Enterobacterales (K. pneumoniae, E. coli, Enterobacter cloacae, Providencia stuartii, Serratia marcescens, Citrobacter freundii)*	30 days
44	Tumbarello *et al.* [63]	37	65 [31-71]	**Mono**: FMC, TGC, GTC, CTN, AMC **Multiple:** MRM/VRB+2 others	Lungs, intra-abdominal, urinary tract, skin and soft tissue, bloodstream	*Klebsiella pneumoniae*	N/A
45	Zheng *et al.* [33]	164	65	**Mono:** CAZ/AVI **Dual:** CAZ/AVI+CBM, CAZ/AVI+TGC, CAZ/AVI+AMC, CAZ/AVI+FMC	Bloodstream, urinary tract, lung, intra-abdominal, others	*Klebsiella pneumoniae*	30 days
46	Cheng *et al.* [64]	98	61.58 (19.07)	**Mono:** Not elaborated **Dual:** mono+TGC, mono+CBM	Lung, blood, others	*Klebsiella pneumoniae*	30 days
47	Önal *et al.* [34]	62	64.68 (3.15)	**Dual:** FMC+MRM, PMC+PMN, FMC+AGS, FMC+Others **Multiple:** FMC+MRM+PMN, FMC+MRM+AGS, FMC+PMN+AGS, Others	lung dan bloodstream	*Klebsiella pneumoniae*	30 days
48	Zhang *et al.* [65]	94	38 [25-49]	**Mono:** CAZ/AVI, PMB **Dual:** CAZ/AVI+ATM, CAZ/AVI+TGC, TGC+AGS, TGC+FMC, TGC+ATM, TGC+ CBM, AGS+ CBM, FQL+CBM, AGS+FQL **Triple:** CAZ/AVI+ATM+TGC, CAZ/AVI+ATM+AGS, CAZ/AVI+ATM+PMB, TGC+AGS+ CBM, TGC+AGS+FQL, PMB+TGC+AGS/FQL, PMB+TGC+CBM, PMB+TGC+ATM	Bloodstream	*Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae, Raultella planticola*	30 days
49	Jaber *et al.* [35]	114	71 [20.0-102.0]	**Mono:** CAZ/AVI, AGS, AZT, CTN, TGC, MRM **Dual:** Not elaborated **Triple:** Not elaborated	Bloodstream, lung, urinary tract, soft tissue	*Klebsiella pneumoniae*	30 days

No.	**Study**	**N**	**Age, Mean (SD)/Median [*range/IQR*]**	**Regimens**	**Type of infection**	**Type of bacteria**	**Observation length**
50	Katip *et al.* [66]	220	[18-100]	**Mono:** CTN **Dual:** CTN+FMC	Bloodstream, urinary tract, Lung, others	*Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae*	30 days
51	Li *et al.* [36]	25	52.1 (15.7)	**Mono:** TGC, CTN, CAZ/AVI **Dual:** Not elaborated	Lung, abdominal, urinary tract, soft tissue	*Klebsiella pneumoniae*	30 days

Noted: n, total sample; CTN, Colistin; TGC, Tigecycline; PMB, Polymyxin B; GTC, Gentamicin; CBM, Carbapenem; AMC, Amikacin; FMC, Fosfomycin; BL/BLI, Beta-lactamase Inhibitor; AGS, Aminoglycoside; QNL, Quinolone; MRM, Meropenem; CFM, Cefepime; AZT, Aztreonam; FQL, Fluoroquinolone; CAZ/AVI, Ceftazidime/Avibactam; STX, Sulfamethoxazole; MXF, Moxifloxacin; LTX, Levofloxacin; PPC, Piperacillin; CLIN, Clindamycin; IMP, Imipenem; RIF, Rifampicin; ETP, Ertapenem; TTC, Tetracycline; ATM, Aztreonam; LVX, Levofloxacin; MNC, Minocycline; PMC, Polymyxin C; PMN, Polymyxin; CEF, Cephalosporin; SFM, Sulfonamide; CPF, Ciprofloxacin; RIF, RIF, Rifampicin; IMP, Imipenem; MXF, Moxifloxacin; TZB, Tazobactam; CLIN, Clindamycin; LZD, Linezolid; CMX, Cefminox; VRB, Vaborbactam; CLX, Colixin; N/A, not available.