Systematic Reviews

RESEARCH

Open Access

Efficiency of combination therapy versus monotherapy for the treatment of infections due to carbapenem-resistant Gram-negative bacteria: a systematic review and meta-analysis

Chengcheng Lai[1†], Zijun Ma[1†], Jun Zhang[2], Junjun Wang[1], Jinghui Wang[1], Zhuanghao Wu[3] and Yonggang Luo[3*]

Abstract

Background For resistant Gram-positive bacteria, evidence suggests that combination therapy is more effective. However, for resistant Gram-negative bacteria, no consensus has been reached. This study aims to comprehensively summarize the evidence and evaluate the impact of combination versus monotherapy on infections caused by carbapenem-resistant Gram-negative bacteria (CRGNB).

Methods A systematic search was conducted in PubMed, Cochrane library, Web of Science, and Embase up to June 15, 2024, to identify relevant studies. This study included comparisons of monotherapy and combination therapy for treating infections caused by CRGNB. Topical antibiotics (i.e., inhalational or intratracheal administration) and monotherapy with sulbactam/relebactam was excluded. The primary outcome was mortality, and the secondary outcomes were clinical success and microbiological eradication. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated in order to systematically assess effect of treatment on mortality, clinical success and microbiological eradication. Subgroup analyses, publication bias tests, and sensitivity analyses were also performed.

Results A total of 62 studies, including 8342 participants, were analyzed, comprising 7 randomized controlled trials and 55 non-randomized studies. Monotherapy was associated with higher mortality (OR = 1.29, 95%CI: 1.11–1.51), lower clinical success (OR = 0.74, 95%CI: 0.56–0.98), and lower microbiological eradication (OR = 0.71, 95%CI: 0.55–0.91) compared to combination therapy for CRGNB infections. Specifically, patients with carbapenem-resistant *Enterobacteriaceae* (CRE) infections receiving monotherapy had higher mortality (OR = 1.50, 95%CI: 1.15–1.95), comparable clinical success (OR = 0.57,95%CI: 0.28–1.16), and lower microbiological eradication (OR = 0.48,95%CI:0.25–0.91) than those receiving combination therapy. For carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections, no significant differences were observed in mortality (OR = 1.15.95%CI: 0.90–1.47), clinical success (OR = 0.95,95%CI: 0.74–1.24) and microbiological eradication (OR = 0.78,95%CI: 0.54–1.12).

[†]Chengcheng Lai and Zijun Ma contributed equally to this work.

*Correspondence:
Yonggang Luo
luoyg_514@126.com
Full list of author information is available at the end of the article

Conclusions Monotherapy or combination therapy is controversial. The systematic review and meta-analysis suggested that monotherapy is associated with higher mortality, lower clinical success, and lower microbiological eradication for treating infection caused by CRGNB. The available evidence suggests that treatment should be selected based on the specific bacteria and antibiotic used. Monotherapy for CRE infections may lead to adverse outcomes. For CRAB infections, no significant differences were found between combination therapy and monotherapy.

Systematic review registration PROSPERO CRD42022331861.

Keywords Combination therapy, Monotherapy, Carbapenem-resistant Gram-negative bacteria, Carbapenem-resistant *Enterobacteriaceae*

Introduction

Carbapenem-resistant Gram-negative pathogens carry a higher risk of mortality and morbidity compared to their carbapenem-susceptible pathogens [1–3].The increasing number of reports indicating high mortality from carbapenem-resistant Gram-negative infections has raised significant concerns [4]. Clinical physicians face challenges in selecting appropriate antimicrobials due to the complexity of empiric and guided antibiotic therapy. It seems difficult to introduce new antibiotics or replace existing ones, making the optimization of antibiotic utilization imperative.

For resistant Gram-positive cocci, such as Methicillin-resistant *Staphylococcus aureus* (MRSA), an increasing body of evidence supports the superiority of combination therapy over monotherapy [5]. This has led to the broader application of combination therapy for resistant Gram-negative bacilli. Numerous studies have confirmed that the use of more than one antibiotic active in vitro against the causative organism leads to lower mortality rates in infections caused by Gram-negative bacteria [6–8]. Combination therapy could prevent the development of resistance, achieve higher clinical improvement, and allow the use of lower doses or shorter treatment durations [9].

In recent years, numerous clinical studies have emerged comparing monotherapy and combination therapy, yielding divergent conclusions. Combination therapy is a common strategy for treating multidrug-resistant infections. Despite the strong rationale for improving efficacy and reducing resistance development, the evidence supporting this approach remains controversial [10]. There is still insufficient evidence to prove that combination therapy is superior to monotherapy. The nation that "The more antibiotics, the better" is not convincing. Combination therapy may lead to a higher incidence of adverse events, such as nephrotoxicity. Small-sized meta-analyses indicate that combination therapy is not superior to monotherapy [11, 12].

Combination therapy or monotherapy? To choose an anti-infective treatment regimen, recently, numerous recent studies and mate-analyses on infections has emerged [13–24]. There is no consensus on whether combination therapy is not superior to monotherapy. Choosing the appropriate treatment for infection patients is challenging; understanding which antibiotics to use, for which organisms, and in what combinations is crucial. We present the findings of a systematic review and meta-analysis aimed at determining whether combination antimicrobial therapy reduces mortality in patients with infections caused by carbapenem-resistant Gram-negative bacteria (CRGNB). To the best of our knowledge, this is the first large, comprehensive meta-analysis on infections due to CRGNB.

Methods

Data sources

The protocol was prospectively registered on PROSPERO with the registration number CRD42022331861. The systematic review was conducted and presented according to the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [25, 26]. We searched PubMed, Cochrane library, Web of Science, and Embase to identify published studies up to March 15, 2022, without language restrictions. We subsequently updated our search until June 15, 2024. The following keywords were searched in combination: Gram-negative bacilli, *Enterobacteriaceae*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Escherichia coli*, *Salmonella*, *Shigella*, *Proteus*, *Serratia*, *Citrobacter*, *Pseudomonas aeruginosa*, resistan*, carbapenem, imipenem, meropenem, ertapenem, doripenem. The full search strategy is available in the Additional File 2. Ethics board approval was no necessity for a meta-analysis of previously published studies.

Eligibility criteria

Studies were included if they compared monotherapy regimens with combination therapy regimens for the treatment of infections caused by CRGNB. Eligible studies had at least 10 participants and endpoints of mortality and/or clinical/microbiological response. We included but was not limited to randomized controlled trials (RCTs), retrospective, and prospective studies. Studies

with significant differences in the number of participants between experimental and control groups were excluded. Due to the controversial efficiency of topical antibiotics (i.e., inhalational or intratracheal administration), we only considered interventions administered or orally. Intravenous administration includes bolus and infusions. In most of the articles, the route of intravenous administration was not further classified. Monotherapy with sulbactam/relebactam was deemed ineligible due to the indistinguishability between beta-lactamase/beta-lactamase inhibitors and beta-lactamase inhibitors. Trials involving animals, in vitro studies, or healthy human subjects were excluded, as were case reports, review articles, and conference abstracts.

Population

We included participants of studies with infections rather than colonization due to CRGNB and with the age of at least 16.

Definitions and outcomes

Monotherapy (MT) is defined as the administration of a single antibiotic agent, while combination therapy (CT) involves the use of two or more antibiotic agents. These can include standardized antibiotic regimens (appropriate dosage and frequency) and non-standardized regimens (inappropriate dosage and frequency). Carbapenems resistance is defined as non-susceptibility to any carbapenem antibiotics, including ertapenem, meropenem, imipenem, and doripenem. Antimicrobial sensitivity tests were conducted using disc diffusion or broth/agar dilution minimum inhibitory concentration (MIC) tests. The MIC cut-off values varied across different studies. The specific MIC standards referenced by each study are detailed in eTable 3 of the Additional file 2.

The primary outcome was mortality, including all-cause mortality and infection-related mortality at the end of the treatment (or at a certain time point in the process of treatment). The secondary outcomes were clinical success and microbiological eradication at the end of the treatment (or at a certain time point in the process of treatment). When data regarding outcomes at the end of treatment or discharge were not provided, outcomes at the end of follow-up were extracted.

Data selection and extraction

Citation management was performed using Endnote X9 (Clarivate). Two reviewers (L.C.C. and L.Y.G.) searched for and examined relevant studies independently. Any controversial issue was resolved through full discussion and decided by the author (L.C.C.) if necessary. The following data was extracted from every research: (1) Characteristics of the study such as author, country, year, study design, number of arms, and period of follow-up; (2) characteristics of settings (i.e., type of wards, admitted in ICU) and participant such as age range, gender, number of patients included in the analysis, type of infection; (3) type of intervention and type of comparator(s) such as concomitant antimicrobial intervention characteristics; and (4) outcomes measure including mortality, clinical success, and microbiological eradication.

Risk of *bias* assessment and quality assessment

Two authors (L.C.C. and M.Z.J.) independently assessed the bias of RCTs by version 2 (RoB 2) tool proposed by the revised Cochrane risk of bias [27] and non-randomized studies interventions (NRSIs) with Methodological Index for Non-randomized Studies (MINORS) terms [28]. The Cochrane risk of bias, RoB 2.0, contains several aspects: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. A summary of our risk of bias evaluations with the Cochrane tool is presented in the Additional File 2 (eFigure1). There are 12 evaluation indicators and each item is rated 0–2 points in the MINORS tool. At the same time, the two independently assessed the quality of evidence at the primary outcome by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Disagreements were resolved by consensus.

Statistical analyses

The meta-analysis was performed with RevMan for Windows, version 5.4.1 and Stata 16.0. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated regarding all outcomes. Statistical heterogeneity among studies was assessed using a $\chi 2$ test ($P < 0.10$ was defined to indicate significant heterogeneity) and I^2 ($I^2 > 50\%$ was defined to indicate significant heterogeneity). The Mantel–Haenszel fixed effect model (FEM) was used when there was no significant statistical heterogeneity between the studies; otherwise, the random effects model was used as appropriate. The test of publication bias was assessed by egger's test with Stata 16.0. We conducted sensitivity analyses, Labbe Graph and Galbraith Plot to check for heterogeneity. For each subgroup analysis, we used random-effects meta-regression to investigate the association of subgroup characteristics with the intervention effect. To investigate potential microorganism-specific effects, we also did post-hoc exploratory subgroup analyses by bacterial type.

Results

Studies characteristics

The search process in four databases generated 11,077 articles, following updating our search until June 15, 2024, and included 10 additional trials (Fig. 1). Sixty-two citations were considered eligible for the analysis at last [11, 29–89]. Reasons for exclusion were shown in the Additional File 2 (eTable2).

The characteristics of the eligible studies are presented in Table 1 and Additional File 2 (eTable3). Seven studies were RCTs [40, 61, 62, 65, 66, 86, 87], 55 were NRSIs [11, 29–39, 41–60, 63, 64, 67–85, 88, 89]. Among these studies, thirty-two studies reported infections due to Carbapenem-resistant Enterobacteriaceae (CRE) [11, 29–31, 33–37, 39, 41, 43–46, 49, 51–53, 55, 59, 60, 68–74, 76, 77, 83]. Sixty studies reported mortality [11, 29–32, 34–43, 45–89], and twenty-four studies reported clinical response [29, 32, 33, 38, 44, 45, 54, 57, 61–63, 66, 67, 69, 71, 77, 80–83, 85–88], and twenty-three studies reported microbiological response [29, 36, 40, 44, 45, 54, 57, 61–67, 77, 81–87, 89]. Ten studies made adjustments for mortality and showed adjusted OR or RR [11, 30, 32, 35, 46, 54, 57–60]. Twenty-eight studies evaluated patients with blood-stream infection/bacteremia (BSI) (including 27 studies only reporting BSI and one study reporting BSI subgroup) [29–32, 35, 37, 38, 41–43, 48, 49, 52, 53, 55, 56, 58–60, 64, 68, 70, 71, 73–77], whereas five studies patients with hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) [34, 39, 61, 62, 67], one study patients with intra-abdominal infection (IAI) [79], two studies patients with urinary tract infection (UTI) [33, 36], four studies patients with pneumonia [63, 78, 80, 82], two study not reported [50, 57], and the remaining twenty-one studied patients with several types of infections [11, 31, 40, 44–47, 51, 54, 65, 66, 69, 72, 81, 83–89]. Twenty-seven studies focused on a particular microorganism, nineteen with *K. pneumoniae* [29, 30, 37, 39, 43, 46, 49, 51–53, 59, 60, 68, 71–74, 77, 84], sixteen with *A. baumannii* [32, 40, 47, 54, 56–58, 61–63, 65, 67, 78, 79, 81, 87], and one with Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) [88]. The remainder included multiple species of Gram-negative bacilli [11, 31, 33–36, 38, 41, 42, 44, 45, 48, 50, 55, 64,

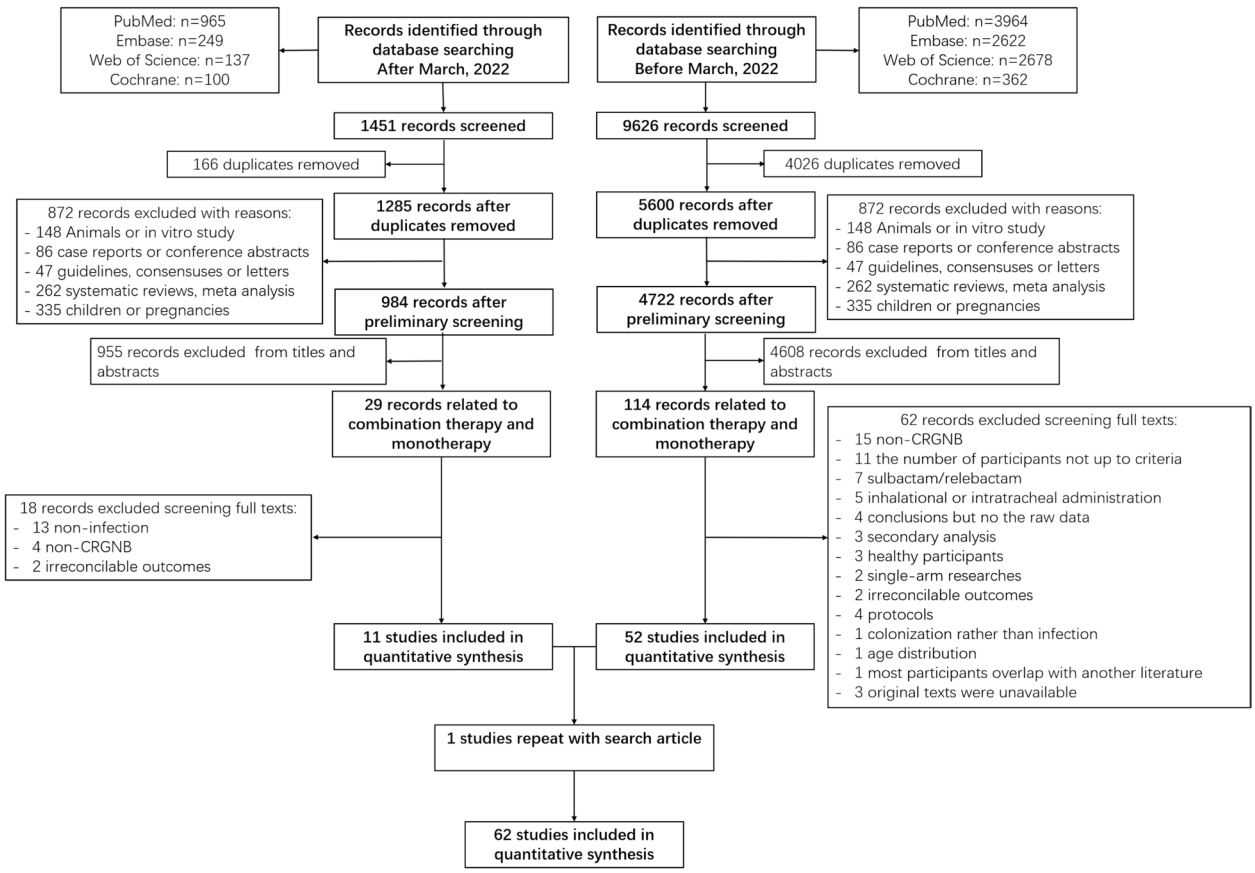

Fig. 1 Flow chart showing the process of literature screening for antibiotic combination therapy versus monotherapy for the treatment of infections due to carbapenem-resistant Gram-negative bacteria based on eligibility criteria

Table 1 Characteristics of studies included in the meta-analysis

Author, year	Type of study	Male (*n*, %)	Organisms	Susceptibility (breakpoints)	Style of infection (%)	Treatment (CT)	Number of patients
Lee 2020	Single-center, retrospective study	109 (64)	CRKP	MIC ≥ 2 for ertapenem or ≥ 4 mg/L for meropenem, or imipenem	Bacteremia (100)	More than one agent as 72 h after bacteremia onset	140
Qureshi 2012	Multicenter, retrospective study	15 (44)	CRKP	the breakpoints published by CLSI in 2009 or 2011	Bacteremia (100)	Two antimicrobials with Gram-negative activity for at least 48 h after the susceptibility results were available	34
Oliveira 2014	Multicenter, retrospective study	62 (53)	CRE	MIC ≥ 4 μg/ml for meropenem or imipenem, MIC ≥ 2 μg/ml, according to 2010 CLSI revised breakpoints	Bacteremia, and others	Use of more than one antimicrobial drug for Gram-negative bacteria	118
Park 2019	Single-center, retrospective study	42 (59)	CRAB	NR	Bacteremia (100)	Colistin/meropenem	71
Freire 2019	Single-center, retrospective study	NR	CRE	NR	UTIs (100)	The use of at least two drugs in the targeted therapy, regardless of their in vitro sensitivity	23
Tuon 2016	Single-center, retrospective study	NR	CRE	CLSI 2013	VAP (100)	At least two active drugs	83
Wang 2018	Multicenter, retrospective study	NR	CRE	CLSI -M7-A10 and CLSI-M100-S28	Bacteremia (100)	At least two active drugs	98
Önal 2019	Single-center, retrospective study	66(66)	CRE	EUCAST criteria	UTIs (100)	At least two drugs	100
LIAO 2015	Single-center, retrospective study	79 (76)	CRKP	NR	Sepsis (100)	At least two drugs	104
Tan 2020	Single-center, retrospective study	139 (79)	CRGNB	CLSI criteria	BSI (100)	Two or more antibiotics	175
Abdelsalam 2018	Single-center, prospective randomized study	28 (47)	CRKP	CLSI 2011	HAP, VAP	Colistin/meropenem	60
Claudia 2016	Single-center, retrospective study	88 (69)	CRE	CLSI 2012	Pneumonia, UTIs, BSI, tissue infection, IAI, sepsis	The use of more than two drugs	127
Sirijatuphat 2014	Single-center, prospective RCT study	44 (47)	CRAB	NR	Pneumonia, BSI, UTIs, skin/ tissue infection, IAI, CNSI, others	Colistin/fosfomycin	94
P.Nadales 2019	Multicenter, retrospective study	NR	CPE	CLSI 2015	BSI (100)	It included 2 or more active drugs	165
Wang 2016	Single-center, prospective study	NR	CRGNB	CLSI	BSI (100)	Two or more active drugs	138
Tumbarello 2012	Multicenter, retrospective study	73 (58)	CPKP	CLSI 2011	BSI (100)	At least 2 vitro-active drugs	125

Table 1 (continued)

Author, year	Type of study	Male (*n*, %)	Organisms	Susceptibility (breakpoints)	Style of infection (%)	Treatment (CT)	Number of patients
RIHANI 2012	Single-center, retrospective study	NR	CPE	CLSI 2010	BSI, pneumonia, tissue infection, UTIs	2 or more antimicrobial agents gave simultaneously for at least 48 h	22
Machuca 2017	Single-center, prospective study	57 (55)	CRKP	All the cases MIC ≥ 64 mg/L (high-level meropenem)	Pneumonia, BSI, UTIs	The regimen included 2 or 3 in vitro active drugs	104
L.Corte´s 2014	Multicenter, retrospective study	NR	CRAB	CLSI 2010	Pneumonia, tissue and skin infection, UTIs, IAI, and others	Therapy with two or more active drugs	94
Ghafur 2017	Single-center, retrospective study	58 (64)	CRGNB	CLSI	BSI (100)	Two or more drugs	91
Tumbarello 2015	Multicenter, retrospective study	417 (63)	KPC-producing KPN	EUCAST	BSI (100)	At least two drugs displaying in vitro activity against the isolate	661
Capone 2012	Multicenter, prospective study	60 (62)	CRKP	EUCAST	UTIs, BSI, RTI, skin/tissues infection, IAI	Two or more active drugs	91
Katip 2020	Single-center, retrospective study	197 (61)	CRAB	CLSI 2015	Pneumonia, bacteremia, UTIs, others	Colistin/meropenem	324
G.Gutiérrez 2017	Multicenter, retrospective study	197 (57)	CPE	CLSI 2012 and local laboratory	BSI (100)	Two or more appropriate drugs	343
Niu 2019	Single-center, retrospective study	55 (26)	CRAB	CLSI M100(2018)	BSI (100)	Cefoperazone-sulbactam combination therapy	75
Katip 2020*	Single-center, retrospective study	90 (36)	CRAB	CLSI M100-S25	NR	Colistin/meropenem	248
Amat 2017	Multicenter, retrospective study	74 (63)	CRAB	CLSI M100-S22	Bacteremia (100)	Tigecycline/colistin	118
Medeiros 2018	Single-center, retrospective study	53 (65)	CPKP	CLSI M100-S21	BSI (100)	Two or more in vitro active agents	82
G.Simmonds 2016	Multicenter, retrospective study	87 (62)	CRKP	CLSI M100-S25	BSI (100)	SAA plus a BL, MAA without or plus a BL	141
AYDEMIR 2012	Single-center, prospective RCT	30 (70)	CRAB	CLSI 2011	VAP (100)	Colistin and rifampicin	43
Makris 2018	Multicenter, prospective RCT	27 (69)	CRAB	NR	VAP (100)	Colistin and ampicillin-sulbactam	39
Shi 2019	Single-center, prospective study	114 (71)	CRAB	CLSI M100	Pneumonia (100)	Colistin and carbapenem	160
Park 2020	Single-center, prospective study	70 (83)	CRGNB	Meropenem MIC > 8 mg/L	Bacteremia (100)	Colistin and other antibiotics against G- and/or G + bacteria	84
Paul 2018	Multicenter, prospective RCT	151 (37)	CRE	EUCAST 2012	bacteremia, VAP, HAP, UTIs	Colistin and meropenem	406

Table 1 (continued)

Author, year	Type of study	Male (*n*, %)	Organisms	Susceptibility (breakpoints)	Style of infection (%)	Treatment (CT)	Number of patients
Yilmaz 2015	Single-center, retrospective study	23 (46)	CRKP	CLSI M100-S21	VAP (100)	Colistin and carbapenem	50
Zhang 2020	Single-center, retrospective study	60 (71)	CRKP	EUCAST	BSI (100)	Two or more drugs	78
Villegas 2016	Multicenter, retrospective study	NR	CPE	CLSI 2014	BSI (100)	Two or more active definitive therapy	37
Karaiskos 2020	Multicenter, prospective study	109 (74)	CRKP	EUCAST	BSI, UTIs, HAP/VAP, IAI, and others	Targeted therapy CAZ-AVI in combination with at least another active agent	147
Tofas 2016	Multicenter, retrospective study	NR	CRKP	EUCAST	BSI (100)	Treatment with two or more in vitro active agents	40
Porwal 2014	Single-center, retrospective study	NR	CRGNB	NR	Bacteremia (100)	Two or more drugs	41
Zhou 2021	Multicenter, prospective study	NR		CLSI M100 S30	BSI (100)	More than one in vitro active antimicrobial treatment	135
Tsai 2021	Single-center, retrospective study	59(50)		CLSI 2021	Bacteremia (100)	At least one or more drugs with in vitro activity against the blood isolates	203
Liang 2017	Multicenter, retrospective study	NR	CRAB	EUCAST	Pneumonia	Two or more drugs	217
Chusri 2019	Single-center, retrospective study	16 (57)	CRAB	Carbapenem MIC ≥ 16 μg/ml was used as the resistance breakpoint	IAI (100)	Tigecycline/colistin	28
Tumbarello 2018	Multicenter, retrospective study	135 (65)	KPC-KPN	EUCAST	Bacteremia (100)	Two or more drugs	208
Shields 2017	Single-center, prospective study	NR	CRKP	CLSI	Bacteremia (100)	CAZ-AVI and gentamicin	13
Madeline 2017	Multicenter, prospective study	36 (60)	CRE	CLSI 2015	Bacteremia, UTIs, pneumonia, wound, IAI, bone infection		60
Cristina 2018	Single-center, retrospective study	19 (83)	CRE	EUCAST	BSI, UTIs, RTI, Osteomyelitis, IAI	CAZ-AVI with colistin/amikacin/colistin or two of these drugs	24
Daikos 2014	Multicenter, retrospective study	103 (59)	CPKP	EUCAST	BSI (100)	Treatment with two or more in vitro active agents	175
G.Padilla 2019	Single-center, retrospective study	NR	CRKP	EUCAST	Sepsis (100)	Tigecycline/gentamicin	37
Hager 2020	Single-center, retrospective study	NR	CRGNB	NR	NR	Colistin combination antibiotic regimen	65

Table 1 (continued)

Author, year	Type of study	Male (*n*, %)	Organisms	Susceptibility (breakpoints)	Style of infection (%)	Treatment (CT)	Number of patients
D.Mangoni 2013	Multicenter, RCT	137 (66)	CRAB	CLSI M100-S20	VAP, BSI, HAP, complicated IAI	Colistin and rifampicin	209
Li 2024	Single-center, retrospective study	62 (75)	CRGNB	CLSI M100-M129	BSI, IAI, UTI, pneumonia, and others	CAZ-AVI and included at least one other antimicrobial agent administered for ≥ 72 h	83
Chen 2024	Multicenter, retrospective study	180 (65)	CRPA	CLSI	Pneumonia, BSI, UTI, and others	Two or more drugs	279
Sirijatuphat 2022	Single-center, prospective RCT	34 (61)	CRAB	CLSI	Pneumonia, BSI, UTI, IAI, and others	Colistin-sitafloxacin	56
Kaye 2023	Multicenter, RCT	265 (63)	CRGNB	CLSI	Pneumonia, BSI	Colistin in combination with meropenem	423
Hao 2022	Single-center, retrospective study	59 (24)	CRGNB	CLSI M100	HAP, BSI, UTI, acute mentingitis	Intravenous colistin sulfate and other antimicrobial agents	80
Lin 2023	Multicenter, retrospective study	100 (76)	CRKP	CLSI	NR	CAZ/AVI and other anti-GNB antibiotics together for more than 2 days	132
Katip 2024	Single-center, retrospective study	131 (60)	CRE	CLSI	UTI, pneumonia, BSI, and others	Colistin plus fosfomycin	220
Zha 2023	Single-center, retrospective study	112 (69)	CRGNB	EUCAST	pneumonia	Tigecycline plus colistin	162
Federica 2023	Multicenter, retrospective study	30 (75)	CRAB	EUCAST	BSI, pneumonia, UTI, IAI, bone infection, and others	Cefiderocol in combination with other (in vitro active) drugs	38
Chang 2022	Multicenter, retrospective study	274 (75)	CRGNB	CLSI, FDA	Pneumonia	Colistin/tigecycline combined with other drugs	364

RCT randomized controlled trial, *CRE* carbapenem-resistant *Enterobacteriaceae*, *CRAB* carbapenem-resistant *Acinetobacter baumannii*, *CRKP* carbapenem-resistant *Klebsiella pneumoniae*, *KPC Klebsiella pneumoniae* carbapenemase, *CPE* carbapenemase-producing *Enterobacteriaceae*, *MIC* minimum inhibitory concentration, *NR* not reported, *EUCAST* European Committee on Antimicrobial Susceptibility Testing, *CLSI* Clinical and Laboratory Standards, *FDA* Food and Drug Administration, *BSI* blood-stream infection/bacteremia, *IAI* intra-abdominal infection, *RTI* respiratory tract infection, *UTI* urinary tract infection, *HAP* hospital-acquired pneumonia, *VAP* ventilator-associated pneumonia, *CAZ-AVI* ceftazidime-avibactam, *CNSI* central nervous system infections, *SAA* single active agent, *BL* β-lactam antibiotic, *MAA* multiple active agents

66, 69, 70, 75, 76, 80, 82, 83, 85, 86, 89]. Eight studies only included patients admitted to ICU [38, 39, 62, 64, 67, 68, 75, 78].

Treatments of patients with Gram-negative bacteria were definite in twenty-five studies, of which 22 compared colistin monotherapy with colistin-based combination therapy [32, 39, 40, 48, 50, 54, 57, 58, 61–67, 75, 78, 80, 83, 85–87], 6 compared ceftazidime-avibactam with ceftazidime-avibactam-based combination therapy [45, 69, 71, 72, 84, 89]. Several different antimicrobial agents were used in the included studies for the treatment of patients with Gram-negative bacteria; however, the detail provided in each study regarding the specific antimicrobial used varied greatly [79].

Mortality

Sixty studies reported mortality, of which 11 reported 14-day mortality [32, 35, 38, 49, 58, 63, 66, 74, 79, 80, 82], 16 reported 28-day mortality [30, 38, 40, 48, 56, 62, 66–68, 72, 73, 80, 85–88], twenty-six reported 30-day mortality [29, 31, 34, 36, 41, 43, 46, 47, 52, 53, 55, 57–60, 64, 65, 71, 75–77, 79, 81, 83, 84, 89], eight reported infection-related mortality [11, 29, 31, 38, 40, 50, 61, 65], and twelve reported in-hospital mortality [29, 35, 39, 42, 45, 51, 61, 63, 64, 78, 79, 84].

Monotherapy groups had higher mortality than combination therapy for treating patients with CRGNB (a total of 8342 patients, OR = 1.29, 95%CI: 1.11–1.51) (Fig. 2). Funnel plot analysis showed no asymmetry. Publication bias was not detected, as tested using the Egger method (Egger's test $P > 0.05$) (Additional File 2. eFigure2). Moderately significant heterogeneity among articles was detected ($I^2 = 50\%$, $P < 0.01$). The Labbe Graph and Galbraith Plot (Additional File 2. eFigure3 and eFigure4) suggested moderate-strong heterogeneity. Sensitivity analysis was chosen for 50 studies and not observed significant heterogeneous articles. Hence, to search for sources of heterogeneity, we performed subgroup analyses to explore these differences further.

Subgroup analyses found that 30-day overall mortality was significantly higher among trials with monotherapy for treating CRGNB than combination therapy (a total of 3293 patients, OR = 1.42, 95%CI: 1.11–1.82). The attributable mortality (931 patients, OR = 1.27, 95%CI: 0.77–2.08), in-hospital all-cause mortality (1251 patients, OR = 1.08, 95%CI: 0.77–1.53), 14-day all-cause mortality (2283 patients, OR = 1.14, 95%CI: 0.87–1.49), and 28-day all-cause mortality (2566 patients, OR = 1.13, 95%CI: 0.83–1.54) of monotherapy were not significantly different compared with combination therapy (Additional File 2. eFigure5).

Subgroup analyses regarding the types of infections were performed. The types of infections from included studies were mainly BSI, HAP/VAP, IAI, UTI, and pneumonia. Monotherapy showed higher mortality in patients with BSI (3689 patients, OR = 1.69, 95%CI: 1.35–2.11) and HAP/VAP (257 patients, OR = 1.89, 95%CI: 1.08–3.30) than combination therapy. The difference was, there were no significant statistical differences between monotherapy and combination therapy for IAI, UTI, pneumonia, and mixed types of infections (Fig. 3).

Specific treatments were Ceftazidime-Avibactam (CAZ-AVI)-based and colistin-based regimens. There was no significant difference between CAZ-AVI-based combination and monotherapy (459 patients, OR = 0.63, 95%CI: 0.39–1.00) (Additional File 2. eFigure6). Patients with infections due to CRGNB who received colistin had similar mortality to those receiving colistin-based combination therapy (included 7 RCTs and 15 NRSIs pooling 3174 patients, OR = 1.09, 95%CI: 0.94–1.27) (Additional file 2. eFigure7). Monotherapy was similar mortality rate to combination therapy among 1023 patients admitted to ICU in nine studies because there was no significant difference (OR = 1.20, 95%CI: 0.79–1.83) (Additional File 2. eFigure8).

Monotherapy was associated with significantly higher mortality in 53 NRSIs pooling a total of 7071 patients (OR = 1.31, 95%CI: 1.10–1.57). We collected all the adjusted ORs to exclude the influence of confounding factors [11, 30, 32, 35, 46, 54, 57–60]. Meta-analysis of adjusted odds ratios estimated the pooled OR to be 1.61 (95%CI 1.10–2.36, $I^2 = 52\%$, $P < 0.05$), which was higher in the MT Group than CT Group (Fig. 4). Considering various pathogens could influence the result, we planned to divide patients into those with infections with Carbapenem-resistant *Acinetobacter baumannii* (CRAB), CRPA, and CRE regarding the type of microorganism. There was neither research that had been done to study carbapenem-resistant *P. aeruginosa* alone nor separate sub-analysis as well before 2022. Only one research was found studied *P. aeruginosa* during 2024 [88]. Patients with infections due to CRE (a total of 4084 patients, OR = 1.50, 95%CI = 1.15–1.95) who received monotherapy had higher mortality than those receiving combination therapy. There was no significant difference in CRAB (1951 patients, OR = 1.15, 95%CI: 0.90–1.47) (Fig. 5).

Seven RCTs enrolled 1270 patients with infections due to CRGNB, with no statistically significant difference between monotherapy and combination therapy (OR = 1.14, 95%CI: 0.91–1.42). All the RCTs compared colistin with the colistin-based combination. The RCTs did not show statistical heterogeneity ($I^2 = 0$, $P > 0.01$) but the NRSIs showed moderate heterogeneity ($I^2 > 50\%$, $P < 0.01$) (Additional File 2.eFigure9).

No significant differences were observed between the colistin alone and colistin-based combination for

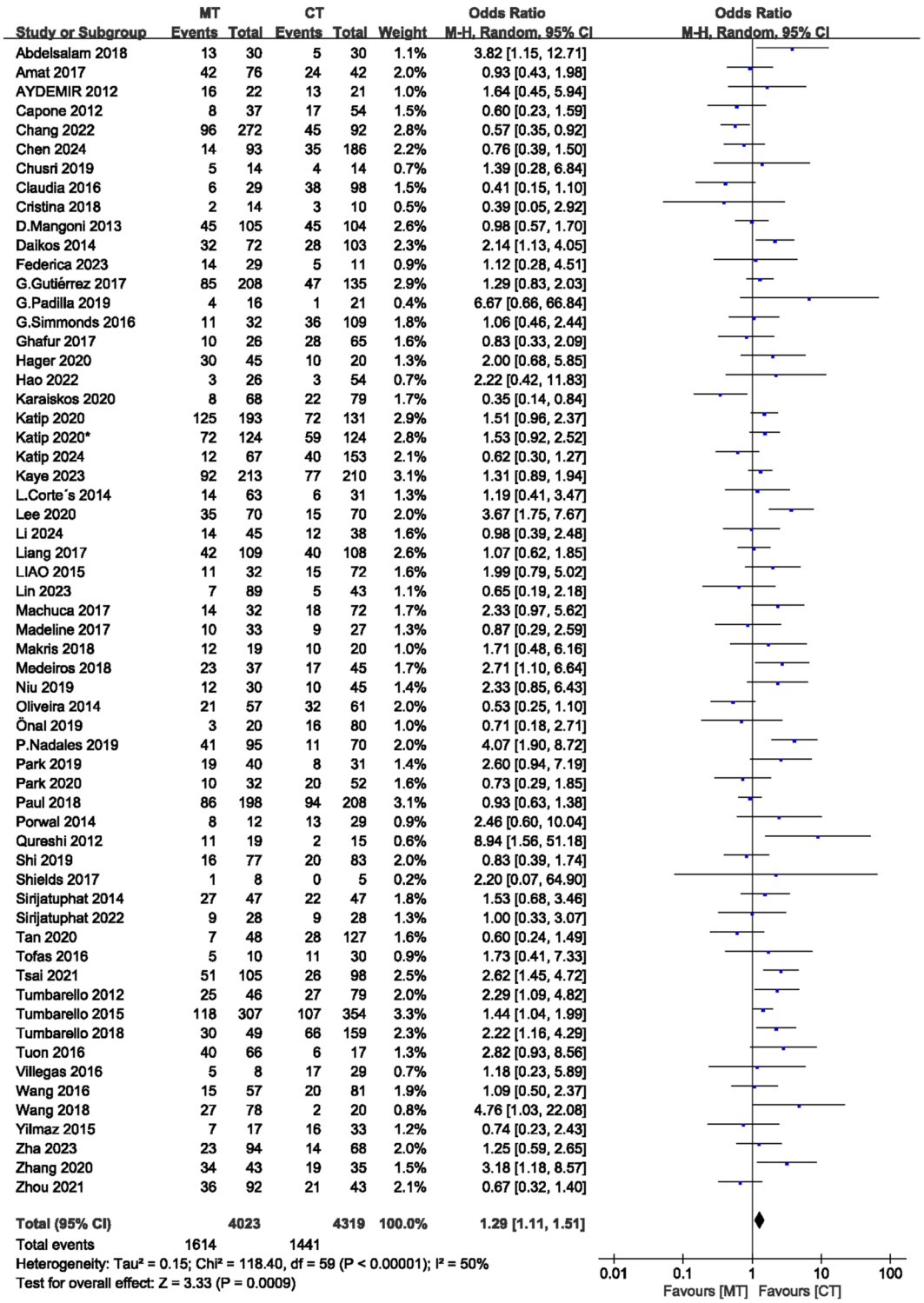

Fig. 2 Comparison of mortality between combination therapy and monotherapy for treating CRGNB

all outcomes, both in RCTs and NRSIs, which indicates that colistin-combination therapy is unpreferred versus colistin alone. There was no publication bias according to the symmetrical funnel plot and Egger's test ($P > 0.05$, Additional File 2.eFigure10). Labbe Graph and Galbraith Plot suggest heterogeneity in our meta-analysis (Additional File 2.eFigure11).

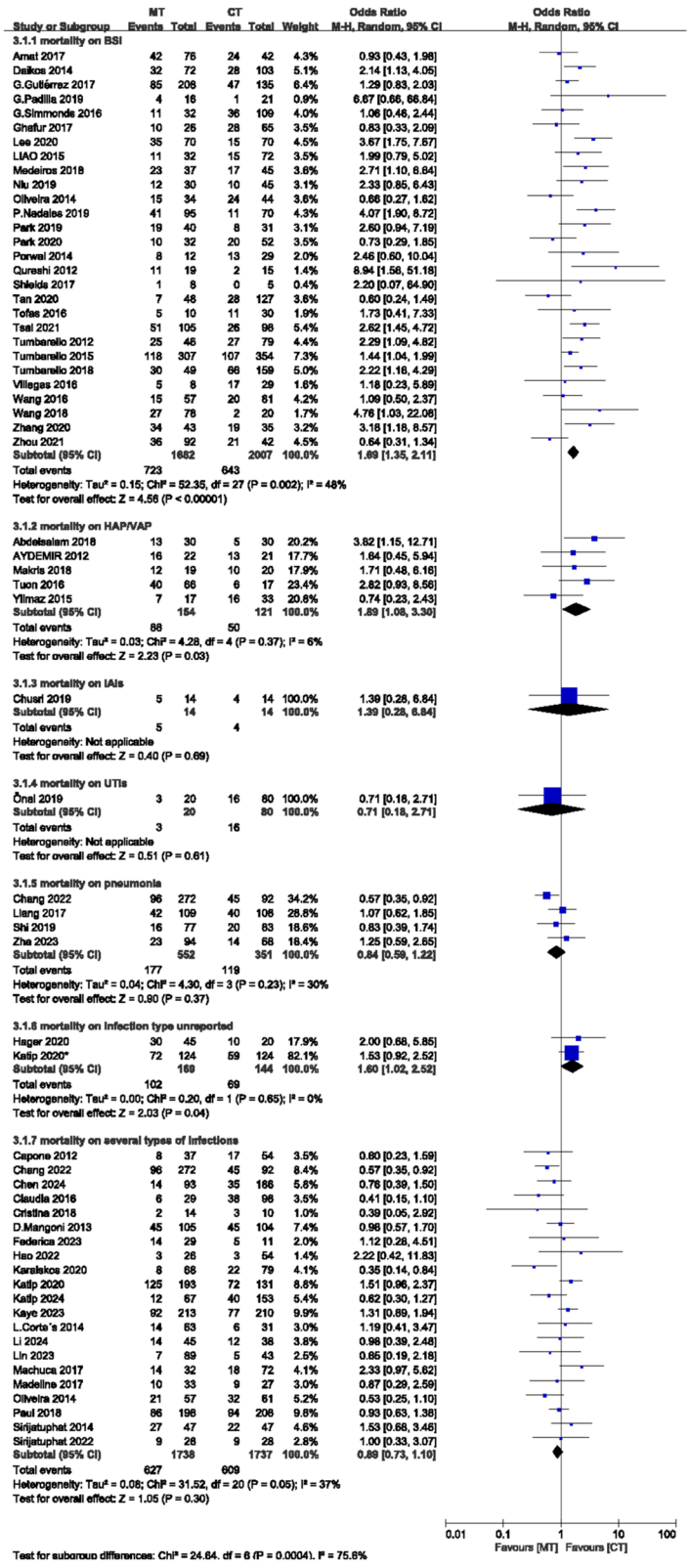

Fig. 3 Subgroup analyses of forest plot regarding the type of infection were performed

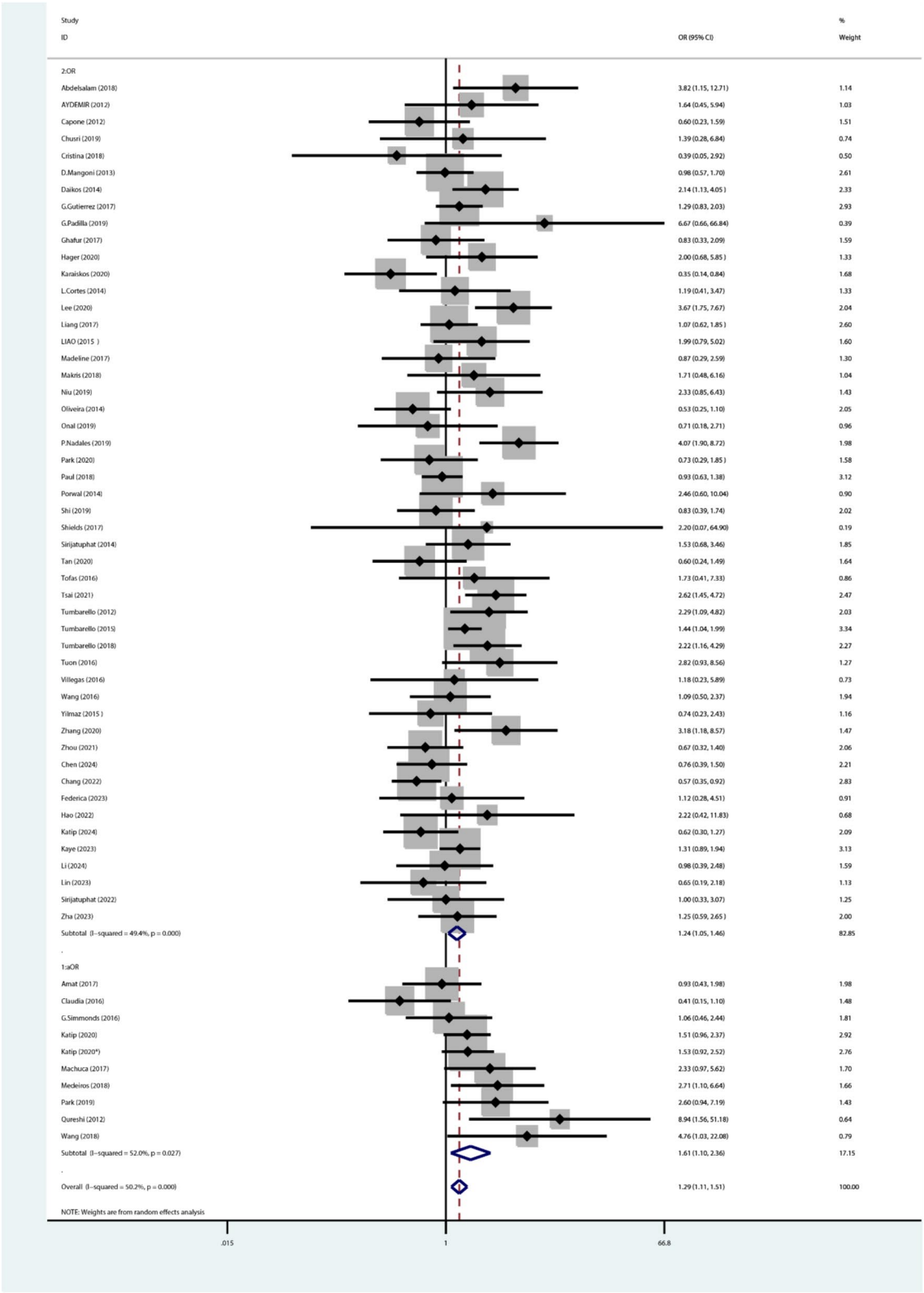

Fig. 4 Subgroup analysis forest plot according to the adjusted mortality was performed

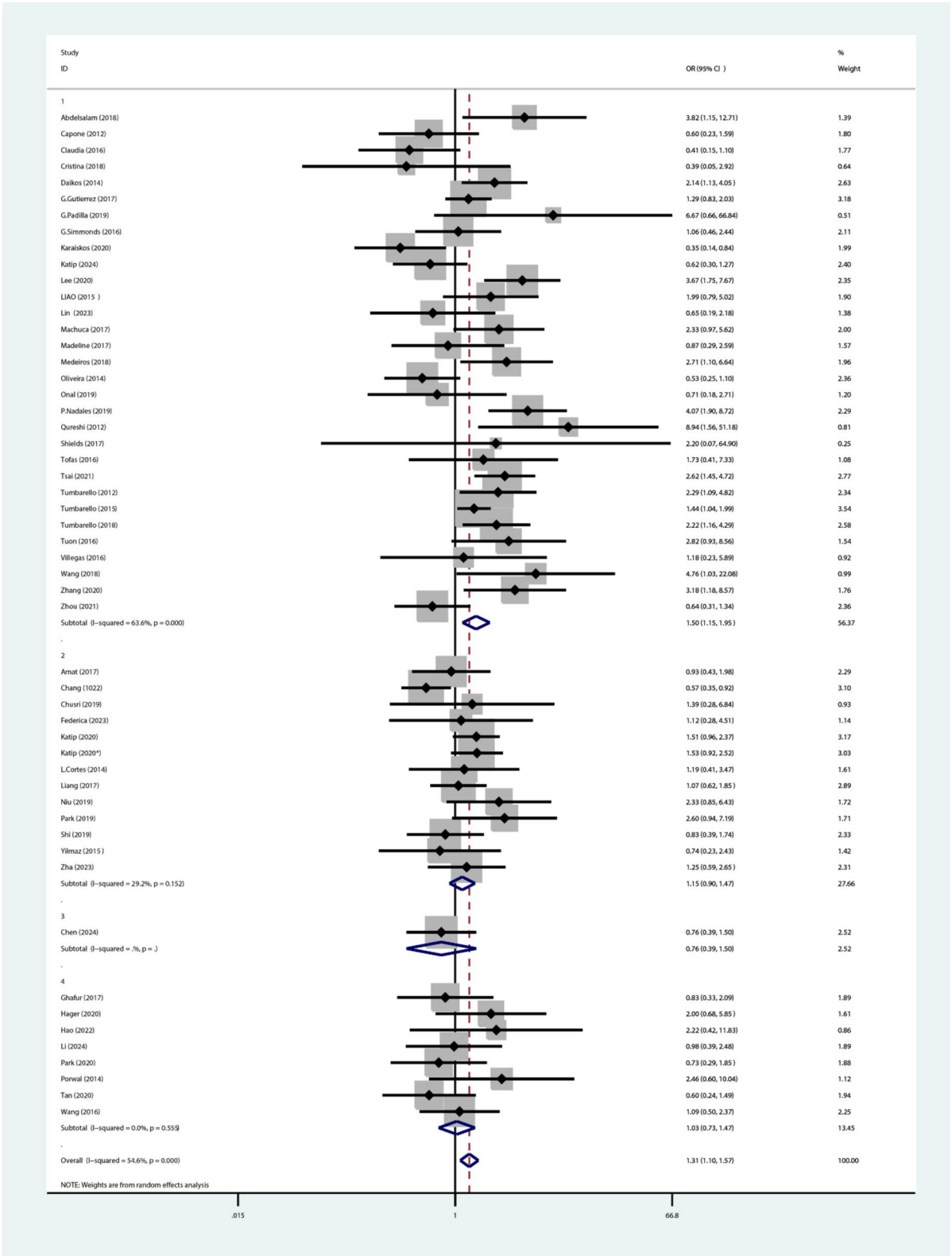

Fig. 5 Comparison of mortality between combination therapy and monotherapy for treating CRE, CRAB, and other CRGNB in 53 NRSIs (group1: CRE, group2: CRAB, group3: CRPA, group4: other CRGNB)

Clinical success

Twenty-four studies consisting of 3625 patients showed that monotherapy was associated with lower clinical success for treating CRGNB (OR = 0.74, 95%CI: 0.56–0.98) (Additional File2.eFigure12). Monotherapy was similar clinical success for treating CRE than combination therapy (705 patients, OR = 0.57, 95%CI: 0.28–1.16). Clinical success showed no significant difference for treating CRAB between MT and CT (1154 patients, OR = 0.95, 95%CI: 0.74–1.24) (Additional File 2.eFigure13). Patients who received colistin in 12 studies seemed to have similar clinical success to the colistin-based combination (2901 patients, OR = 1.00, 95%CI: 0.76–1.32) (Additional File 2.eFigure14). Patients who received CAZ-AVI have similar clinical success to the CAZ-AVI-based combination (259 patients, OR = 0.90, 95%CI: 0.54–1.50).

Microbiological eradication

Twenty-three studies, including 3360 patients, reported microbiological eradication. Microbiological eradication on monotherapy was lower than combination therapy for treating patients due to CRGNB (OR = 0.71, 95%CI: 0.55–0.91) (Additional File 2.eFigure15). Subgroup analyses resulted to different outcomes. Microbiological eradication on monotherapy was lower in NRSIs (2097 patients, OR = 0.71, 95%CI: 0.52–0.96), but no statistically significant difference in RCTs (1263 patients, OR = 0.69, 95%CI: 0.42–1.13).

Seven studies including 866 patients reported microbiological eradication for treating CRE, which suggested that patients with monotherapy had a significantly lower microbiological eradication than those with combination therapy (OR = 0.48, 95%CI: 0.25–0.91). Microbiological eradication showed no difference in monotherapy for treating CRAB MT and CT (1418 patients, OR = 0.78, 95%CI: 0.54–1.12) (Additional File2.eFigure16). Patients receiving colistin alone were similar microbiological eradication to whom received colistin-based combination therapy (1771 patients, OR = 0.70, 95%CI: 0.49–1.01) (Additional File2.eFigure17). Patients who received CAZ-AVI have similar microbiological eradication to the CAZ-AVI-based combination (437 patients, OR = 1.18, 95%CI: 0.79–1.77).

Heterogeneity analysis

In meta-analysis, sensitivity analysis, subgroup analysis, and meta-regression analysis were performed respectively to find the source of heterogeneity. Labbe Graph and Galbraith Plot (Additional File2.eFigure3 and 4) suggested strong heterogeneity in some studies. In the non-randomized trials, the OR value and heterogeneity did not change when any non-randomized trial was excluded. The adjusted ORs were collected and performed a subgroup analysis on the mortality of infected patients caused by CRGNB. The mortality after merging adjusted ORs was higher in the MT Group than CT Group. To analyze heterogeneity, first, 53 non-randomized trials were divided into two groups by infection types: BSIs and other infections. Meta-regression was performed on this variable and found that bloodstream infection was not the source of heterogeneity ($P > 0.05$). Then, monotherapy might be composed of either one certain agent or different antimicrobial agents. Monotherapy was one certain agent or not did not affect the results after meta-regression. In addition, meta-regression and subgroup analyses were performed according to special bacteria. Fifty-three NRSIs were divided into three groups: CRE, CRAB, and other CRGNB. Meta-regression using group (infection type) as covariate suggested that infection type was not the source of heterogeneity ($P > 0.05$, eTable5). At the same time, 53 NRSIs were divided into two groups: group 1 (CRKP) and group 2 (non-CRKP group) by particular microorganism. The difference between the Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) group and the non-CRKP group was significant by meta-regression ($P < 0.05$, eTable6), which is different from CRAB ($P > 0.05$).

Qualitative assessment

To assess the risk of bias for RCTs, we used the revised Cochrane RoB 2 [27]. Additional File 2 supplied eFigure18 to show the assessment of quality. Four trials had an unclear risk, and one trial had a high risk of bias. Previous systematic reviews and meta-analyses used either no formal RoB 2 assessment or the PEDro scale, which combines both reporting and methodological limitations into a single scale. Currently, various tools for evaluating observational research quality methodologies have been used in systematic reviews, while Newcastle–Ottawa [90] and Downs-Black tools [91] are two of the most widely used, which could not fully assess the quality of the articles. We decided to accomplish the quality assessment of NRSIs with the MINORS tool [28]. The full evaluations are provided in the Additional File 2 (eTable4).

Using the GRADE summary of the evidence, the quality of evidence for the primary outcome was moderate. For mortality, we downgraded the evidence by 1 level for serious risk of bias and 1 level for serious imprecision owing to the low numbers of participants (Additional File 2.eFigure19). Both RCTs and NRSIs presented to some extent higher degree of risk.

Discussion

This systematic review and meta-analysis provide a comprehensive comparison between monotherapy and combination therapy for treating infections caused by

carbapenem-resistant Gram-negative bacteria. The findings from 62 studies, encompassing both randomized controlled trials and non-randomized studies, indicate that combination therapy is associated with lower mortality, higher clinical success, and superior microbiological eradication compared to monotherapy. These results have significant implications for clinical decision-making in the management of CRGNB infections, particularly in high-risk patient populations [92, 93].

The primary outcome of this study—mortality—was significantly lower in patients receiving combination therapy. Specifically, the pooled OR for mortality in monotherapy compared to combination therapy was 1.29 (95% CI: 1.11–1.51), indicating a 29% higher risk of death in the monotherapy group. This finding aligns with previous studies that have highlighted the benefits of using multiple antibiotics to target resistant pathogens more effectively. For instance, Tumbarello reported that combination therapy led to significantly better outcomes in patients with bloodstream infections caused by carbapenem-resistant *Klebsiella pneumoniae* [94]. The synergistic effects of combining agents like colistin, meropenem, and tigecycline may account for this improved survival, as each drug targets different mechanisms of bacterial resistance.

In terms of clinical success, our analysis demonstrated that combination therapy was associated with a 26% higher likelihood of successful treatment (OR = 0.74, 95% CI: 0.56–0.98). This is particularly important given the increasing prevalence of multidrug-resistant organisms that limit the effectiveness of single-agent regimens. The use of combination therapy, especially in critically ill patients, has been advocated to both enhance the efficacy of treatment and prevent the development of further resistance. Notably, a study by Gutiérrez-Gutiérrez showed that appropriate combination therapy significantly reduced mortality in patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* (CPE) [55], further supporting the conclusions drawn in our study. The microbiological eradication rates were also higher in the combination therapy group, with a pooled OR of 0.71 (95% CI: 0.55–0.91). This suggests that using multiple antibiotics not only improves patient outcomes but also enhances the ability to completely eliminate the infecting organism. However, it is important to note that the specific combinations of antibiotics used in different studies varied significantly, and not all combinations may provide equal benefits. For example, while colistin-based combinations were frequently used, some studies suggested that adding other agents, such as carbapenems, did not significantly improve outcomes [66, 86]. This highlights the need for more targeted research to determine which specific antibiotic combinations are most effective for different pathogens. The findings of this meta-analysis align with several other systematic reviews and meta-analyses that have compared monotherapy and combination therapy for multidrug-resistant Gram-negative infections. A study by Tamma emphasized that combination therapy was associated with lower mortality in patients with Gram-negative bacterial infections, particularly when at least one of the agents was active in vitro against the pathogen [92]. Similarly, a meta-analysis by Paul found that beta-lactam-aminoglycoside combination therapy was superior to monotherapy in reducing mortality in patients with sepsis [95]. However, some studies have questioned the universal applicability of combination therapy. For example, a Cochrane review by Schmid concluded that there was insufficient evidence to recommend combination therapy over monotherapy in all cases of multidrug-resistant infections, particularly due to the potential for increased toxicity and adverse events [21]. This concern is echoed in our analysis, where some studies indicated that combination therapy, especially those involving nephrotoxic agents like colistin, may lead to higher rates of renal impairment.

In a secondary analysis of the AIDA study, in vitro models involving 171 patients with infections caused by carbapenem-resistant Gram-negative bacteria demonstrated synergism between colistin and carbapenems, supporting the combination treatment of these infections However, the clinical translation of this in vitro synergy was limited. When comparing the outcomes of the synergy group with the antagonism/indifference group, the in vitro synergy between colistin and meropenem did not result in significant clinical benefits [96]. This highlights the complexity of translating laboratory findings into real-world clinical settings, where various factors, including drug pharmacokinetics and host immune responses, can significantly affect treatment outcomes. Previous studies have also examined the limitations of in vitro results when applied to clinical practice. For instance, Paul pointed out that the observed synergistic effects of antibiotics in vitro often fail to manifest in clinical settings because of factors like drug bioavailability, immune status, and underlying patient conditions [97].

One potential solution to this challenge is to incorporate combination susceptibility testing into routine clinical practice. Traditional antibiotic susceptibility testing is performed on individual agents, yet the effectiveness of combination therapies may depend on how these drugs interact within the patient's body. Studies have indicated that combined susceptibility testing can provide more accurate insights into the potential efficacy of combination regimens [9, 98]. This method could help clinicians better predict which combinations of antibiotics will be most effective, especially in

patients with severe infections caused by extensively drug-resistant organisms.

Our meta-analysis also underscores the importance of integrating data from NSRIs alongside RCTs. While RCTs are considered the gold standard for clinical evidence, they are often limited by small sample sizes and strict inclusion criteria, which may not reflect the full spectrum of clinical scenarios. NRSIs, despite their inherent biases, provide valuable insights into real-world clinical practices and outcomes. For example, a large observational study by Park indicated that combination therapy with colistin and meropenem was associated with improved survival rates compared to monotherapy [63], reinforcing the findings of our meta-analysis. However, the interpretation of our results must be approached with caution due to several limitations. The heterogeneity among the included studies—particularly regarding infection types, patient populations, and treatment regimens—introduces a degree of uncertainty. For instance, while combination therapy appeared to be more effective for treating infections caused by *Klebsiella pneumoniae* (OR = 1.50, 95% CI: 1.15–1.95), the same benefit was not observed for *Acinetobacter baumannii* (OR = 1.15, 95% CI: 0.90–1.47). This variability suggests that the efficacy of combination therapy may depend on the specific pathogen involved, as well as the patient's underlying health status and immune response.

Moreover, most of the included studies were observational, which introduces potential biases such as confounding by indication, where sicker patients are more likely to receive combination therapy, thus skewing the results. Although adjusted odds ratios were used in some studies to account for these factors, residual confounding cannot be ruled out. Additionally, the small number of well-powered RCTs limits the strength of the evidence supporting combination therapy. While observational studies offer important real-world insights, their inherent limitations necessitate further investigation through high-quality RCTs.

To definitively establish the advantages of combination therapy over monotherapy, future research should focus on conducting large-scale, well-designed RCTs. These studies should standardize treatment protocols and include combination susceptibility testing to provide more accurate assessments of treatment efficacy. Furthermore, the development of new antibiotics and combination regimens that minimize toxicity—particularly nephrotoxicity associated with colistin—remains a priority. Recent advancements in beta-lactam/beta-lactamase inhibitors, such as ceftazidime-avibactam, have shown promise in treating carbapenem-resistant infections with fewer adverse effects [99].

In conclusion, while the current evidence supports the use of combination therapy for treating CRGNB infections, particularly in cases involving carbapenem-resistant *Enterobacteriaceae* (CRE), clinicians must carefully weigh the benefits against potential risks such as toxicity. More robust clinical trials are needed to refine treatment strategies and optimize outcomes for patients with these challenging infections.

Limitations and implications

Several limitations should be considered when interpreting the results of this meta-analysis. First, the heterogeneity among the included studies was significant, particularly in terms of the types of infections, pathogens, and treatment regimens. For example, while combination therapy appeared to be more beneficial for treating infections caused by *Klebsiella pneumoniae* (OR = 1.50, 95% CI: 1.15–1.95), the same was not observed for *Acinetobacter baumannii* (OR = 1.15, 95% CI: 0.90–1.47). This suggests that the efficacy of combination therapy may vary depending on the specific pathogen and clinical context.

Second, most of the included studies were observational, with only a small proportion being randomized controlled trials. Observational studies are inherently prone to confounding, and despite the use of adjusted odds ratios in some analyses, residual confounding cannot be ruled out. Moreover, the severity of illness, the timing of antibiotic administration, and the appropriateness of empirical therapy were not consistently reported across studies, which could have influenced the outcomes.

Additionally, the use of colistin in combination therapy has been a subject of debate due to its nephrotoxicity. While colistin-based combinations were frequently used in the included studies, there is growing concern about the long-term safety of this agent, particularly in patients with renal impairment. Future studies should explore safer and equally effective alternatives to colistin, such as newer beta-lactam-beta-lactamase inhibitor combinations like ceftazidime-avibactam, which have shown promising results in recent clinical trials.

The findings of this study underscore the importance of tailoring antibiotic therapy to the specific pathogen and patient characteristics. In particular, combination therapy should be strongly considered in patients with bloodstream infections or ventilator-associated pneumonia caused by CRE, as these patients appear to benefit the most from dual-agent therapy. However, for infections caused by *Acinetobacter baumannii*, the choice between monotherapy and combination therapy remains less clear, and further research is needed to clarify the optimal treatment strategy for these infections.

Future research should focus on conducting large-scale, high-quality randomized controlled trials to definitively determine the role of combination therapy in different types of CRGNB infections. Additionally, the development of novel antibiotics and combination regimens that are less toxic than colistin is crucial. As new agents become available, it will be important to incorporate them into combination therapy regimens and evaluate their effectiveness in both clinical and microbiological outcomes.

In conclusion, while this meta-analysis supports the use of combination therapy for CRGNB infections, particularly in cases of CRE, it is important to weigh the potential benefits against the risks of toxicity. Clinicians should consider the specific pathogen, the patient's clinical condition, and the available antibiotic options when selecting a treatment regimen. More research is needed to identify the most effective and safe combinations of antibiotics, especially for infections caused by *Acinetobacter baumannii* and other highly resistant organisms.

Conclusion

Moderate-level RCT results showed no statistical difference between monotherapy and combination therapy, while low-level NRSIs results showed that combination therapy was superior to monotherapy. Overall, the available evidence suggested that treatment should be selected according to the bacteria and antibiotic. CRE infection treated in monotherapy may be adverse outcomes particularly CRKP. CRAB infection had no difference between combination therapy and monotherapy. There was no difference in the incidence of adverse outcomes between colistin or CAZ-AVI monotherapy and combination therapy. Colistin or CAZ-AVI combined with other antibacterial agents is not recommended for carbapenem-resistant gram-negative bacteria. In the absence of large RCT studies, we recommend choosing combination therapy to treat infection due to carbapenem-resistant Enterobacteriaceae after assessing the patient for a range of conditions. More randomized trials are needed for each type of infection to ensure reliable conclusions about the efficacy of treatments.

Abbreviations

CRGNB	Gram-negative bacteremia
CRE	Carbapenem-resistant Enterobacteriaceae
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRKP	Carbapenem-resistant *Klebsiella pneumoniae*
KPC	*Klebsiella pneumoniae* Carbapenemase
CPE	Carbapenemase-producing Enterobacteriaceae
CRPA	Carbapenem-resistant *Pseudomonas aeruginosa*
WHO	World Health Organization
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
MINORS	Methodological Index for Non-randomized Studies
CT	Combination antibiotic therapy
MT	Monotherapy
RCT	Randomized studies trials
RoB 2	Cochrane risk of bias, version 2
NRSIs	Non-randomized studies interventions
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	Intensive care unit
OR	Odds ratio
aOR	Adjusted odds ratio
BSI	Blood-stream infection/bacteremia
HAP	Hospital-acquired pneumonia
VAP	Ventilator-associated pneumonia
IAI	Intra-abdominal infection
UTI	Urinary tract infection
RTI	Respiratory tract infection
CNSI	Central nervous system infections
MIC	Minimum inhibitory concentration
NR	Not reported
EUCAST	European Committee on Antimicrobial Susceptibility Testing
CLSI	Clinical and Laboratory Standards
CAZ-AVI	Ceftazidime-Avibactam
PK	Pharmacokinetics
PD	Pharmacodynamics

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02695-x.

Additional file 1. PRISMA checklist.

Additional file 2. Search strategy, tables and figures.

Acknowledgements

All authors are grateful to reviewers and editors for their help and suggestions.

Authors' contributions

L.C.C. searched for and examined relevant studies, finished analysis, and drafted the work. M.Z.J. and Z.J. finished the acquisition, and interpretation of data, and contributed to writing the manuscript. L.Y.G. searched for and examined relevant studies, contributed to writing the manuscript, substantively revised it, and check the overall quality of the article. W.J.J. created tables, graphs, and made important comments about the creation. W.J.H. and W.Z.H. contributed to writing the manuscript and made a huge contribution to the revision of the article. All authors read and approved the final manuscript. It should be noted that the division of labor is not separate.

Funding

This research was funded by Young and Middle-aged Scientific Technological Innovation Jie-Qing Talent Project (YXKC2021042), Henan Province Key Medical Science and Technology Research Project Co-established by Provincial and Ministerial Authorities (CN)(SBGJ202102081), Henan Province Science and Technology Research Project (CN) (242102311040), and Henan Province Natural Science Foundation Project (CN) (242300420384).

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the specificity of the type of dataset but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Department of General Practice, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China. [2]Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China. [3]Department of Neurosurgical Intensive Care Unit, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

Received: 26 September 2023 Accepted: 27 October 2024
Published online: 19 December 2024

References

1. Cai B, Echols R, Magee G, Arjona Ferreira JC, Morgan G, Ariyasu M, et al. Prevalence of Carbapenem-Resistant Gram-Negative Infections in the United States Predominated by Acinetobacter baumannii and Pseudomonas aeruginosa. Open Forum Infect Dis. 2017;4:ofx176. https://doi.org/10.1093/ofid/ofx176.
2. Maraolo AE, Corcione S, Grossi A, Signori A, Alicino C, Hussein K, et al. The impact of Carbapenem resistance on mortality in patients with Klebsiella pneumoniae bloodstream infection: an individual patient data meta-analysis of 1952 patients. Infect Dis Ther. 2021;10:541–58. https://doi.org/10.1007/s40121-021-00408-8.
3. Jean S-S, Harnod D, Hsueh P-R. Global threat of Carbapenem-resistant gram-negative bacteria. Frontiers in Cellular and Infection Microbiology. 2022;12.https://doi.org/10.3389/fcimb.2022.823684.
4. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. In: WHO, editor. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO: WHO; 2017.
5. Mahjabeen F, et al. An update on treatment options for Methicillin resistant Staphylococcus aureus (MRSA) bacteremia: a systematic review. Cureus. 2022;14:e31486. https://doi.org/10.7759/cureus.31486.
6. Bochud PY, Glauser MP, Calandra T. Antibiotics in sepsis. Intensive Care Med. 2001;27 Suppl 1:S33–48. https://doi.org/10.1007/pl00003796.
7. Kolleff MH. Appropriate antibiotic therapy for ventilator-associated pneumonia and sepsis: a necessity, not an issue for debate. Intensive Care Med. 2003;29:147–9. https://doi.org/10.1007/s00134-002-1614-x.
8. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998;244:379–86. https://doi.org/10.1046/j.1365-2796.1998.00379.x.
9. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev. 2012;25:450–70. https://doi.org/10.1128/CMR.05041-11.
10. Paul M, Bishara J, Levcovich A, Chowers M, Goldberg E, Singer P, et al. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother. 2010;65:1019–27. https://doi.org/10.1093/jac/dkq069.
11. de Maio Carrilho CMD, de Oliveira LM, Gaudereto J, Perozin JS, Urbano MR, Camargo CH, et al. A prospective study of treatment of carbapenem-resistant Enterobacteriaceae infections and risk factors associated with outcome. BMC Infect Dis. 2016;16.https://doi.org/10.1186/s12879-016-1979-z.
12. Amat T, Gutiérrez-Pizarraya A, Machuca I, Gracia-Ahufinger I, Pérez-Nadales E, Torre-Giménez Á, et al. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant Acinetobacter baumannii. Clin Microbiol Infect. 2018;24:630–4. https://doi.org/10.1016/j.cmi.2017.09.016.
13. Cai Y, Wang R, Liang B, Bai N, Liu Y. Systematic review and meta-analysis of the effectiveness and safety of tigecycline for treatment of infectious disease. Antimicrob Agents Chemother. 2011;55:1162–72. https://doi.org/10.1128/aac.01402-10.
14. Hou SY, Wu D, Feng XH. Polymyxin monotherapy versus polymyxin-based combination therapy against carbapenem-resistant Klebsiella pneumoniae: a systematic review and meta-analysis. J Glob Antimicrob Resist. 2020;23:197–202. https://doi.org/10.1016/j.jgar.2020.08.024.
15. Hu Y, Li L, Li W, Xu H, He P, Yan X, et al. Combination antibiotic therapy versus monotherapy for Pseudomonas aeruginosa bacteraemia: a meta-analysis of retrospective and prospective studies. Int J Antimicrob Agents. 2013;42:492–6. https://doi.org/10.1016/j.ijantimicag.2013.09.002.
16. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. J Antimicrob Chemother. 2018;73:22–32. https://doi.org/10.1093/jac/dkx368.
17. Onorato L, Di Caprio G, Signoriello S, Coppola N. Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: a meta-analysis. Int J Antimicrob Agents. 2019;54:735–40. https://doi.org/10.1016/j.ijantimicag.2019.08.025.
18. Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev. 2014;2014:Cd003344. https://doi.org/10.1002/14651858.CD003344.pub3.
19. Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. Cochrane Database Syst Rev. 2003:Cd003038.https://doi.org/10.1002/14651858.Cd003038.
20. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis. 2004;4:519–27. https://doi.org/10.1016/s1473-3099(04)01108-9.
21. Schmid A, Wolfensberger A, Nemeth J, Schreiber PW, Sax H, Kuster SP. Monotherapy versus combination therapy for multidrug-resistant Gram-negative infections: systematic review and meta-analysis. Sci Rep. 2019;9:15290. https://doi.org/10.1038/s41598-019-51711-x.
22. Scudeller L, Righi E, Chiamenti M, Bragantini D, Menchinelli G, Cattaneo P, et al. Systematic review and meta-analysis of in vitro efficacy of antibiotic combination therapy against carbapenem-resistant Gram-negative bacilli. Int J Antimicrob Agents. 2021;57:106344. https://doi.org/10.1016/j.ijantimicag.2021.106344.
23. Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. Lancet Infect Dis. 2011;11:834–44. https://doi.org/10.1016/s1473-3099(11)70177-3.
24. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother. 2017;72:29–39. https://doi.org/10.1093/jac/dkw377.
25. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777–84. https://doi.org/10.7326/m14-2385.
26. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Syst Rev. 2021;10:39. https://doi.org/10.1186/s13643-020-01542-z.
27. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.
28. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. ANZ J Surg. 2003;73:712–6.
29. Lee NY, Tsai CS, Syue LS, Chen PL, Li CW, Li MC, et al. Treatment outcome of bacteremia due to non-Carbapenemase-producing Carbapenem-resistant Klebsiella pneumoniae bacteremia: role of Carbapenem combination therapy. Clin Ther. 2020;42:e33–44. https://doi.org/10.1016/j.clinthera.2020.01.004.
30. Qureshi ZA, Paterson DL, Potoski BA, Kilayko MC, Sandovsky G, Sordillo E, et al. Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother. 2012;56:2108–13. https://doi.org/10.1128/AAC.06268-11.
31. de Oliveira MS, de Assis DB, Freire MP, do Prado GVB, Machado AS, Abdala E, et al. Treatment of KPC-producing Enterobacteriaceae: suboptimal efficacy of polymyxins. Clin Microbiol Infect. 2014;21:179.e1-.e7. https://doi.org/10.1016/j.cmi.2014.07.010.

32. Park SY, Si HJ, Eom JS, Lee JS. Survival of carbapenem-resistant Acinetobacter baumannii bacteremia: colistin monotherapy versus colistin plus meropenem. J Int Med Res. 2019;47:5977–85. https://doi.org/10.1177/0300060519879336.
33. Freire MP, de Oliveira Garcia D, Cury AP, Francisco GR, dos Santos NF, Spadão F, et al. The role of therapy with aminoglycoside in the outcomes of kidney transplant recipients infected with polymyxin- and carbapenem-resistant Enterobacteriaceae. Eur J Clin Microbiol Infect Dis. 2019;38:755–65. https://doi.org/10.1007/s10096-019-03468-4.
34. Tuon FF, Graf ME, Merlini A, Rocha JL, Stallbaum S, Arend LN, et al. Risk factors for mortality in patients with ventilator-associated pneumonia caused by carbapenem-resistant Enterobacteriaceae. Braz J Infect Dis. 2017;21:1–6. https://doi.org/10.1016/j.bjid.2016.09.008.
35. Wang X, Wang Q, Cao B, Sun S, Zhang Y, Gu B, et al. Retrospective observational study from a Chinese network of the impact of combination therapy versus monotherapy on mortality from Carbapenem-resistant Enterobacteriaceae Bacteremia. Antimicrobial Agents Chemother. 2018;63.https://doi.org/10.1128/AAC.01511-18.
36. Onal U, Sipahil OR, Pullukcul H, Yamazhan T, Arda B, Ulusoy S, et al. Retrospective evaluation of the patients with urinary tract infections due to carbapenemase producing Enterobacteriaceae. J Chemother. 2019;32:15–20. https://doi.org/10.1080/1120009X.2019.1688490.
37. Liao Y, Hu GH, Xu YF, Che JP, Luo M, Zhang HM, et al. Retrospective analysis of fosfomycin combinational therapy for sepsis caused by carbapenem-resistant Klebsiella pneumoniae. Exp Ther Med. 2015;13:1003–10. https://doi.org/10.3892/etm.2017.4046.
38. Tan J, Yu W, Wu G, Shen J, Fang Y, Zhu H, et al. A real-world study comparing various antimicrobial regimens for bloodstream infections caused by carbapenem-resistant gram-negative bacilli in a tertiary hospital, Shanghai, China, from 2010 to 2017. Infect Drug Resist. 2020;13:2453–63. https://doi.org/10.2147/IDR.S247378.
39. Abdelsalam MFA, Abdalla MS, El-Abhar HSE. Prospective, comparative clinical study between high-dose colistin monotherapy and colistin-meropenem combination therapy for treatment of hospital-acquired pneumonia and ventilator-associated pneumonia caused by multidrug-resistant Klebsiella pneumoniae. J Glob Antimicrob Resist. 2018;15:127–35. https://doi.org/10.1016/j.jgar.2018.07.003.
40. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother. 2014;58:5598at01. https://doi.org/10.1128/AAC.02435-13.
41. Perez-Nadales E, Gutierrez-Gutierrez B, Natera AM, Abdala E, Reina Magalhaes M, Mularoni A, et al. Predictors of mortality in solid organ transplant recipients with bloodstream infections due to carbapenemase-producing Enterobacterales: the impact of cytomegalovirus disease and lymphopenia. Am J Transplant. 2019;20:1629–41. https://doi.org/10.1111/ajt.15769.
42. Wang W, Jiang T, Zhang W, Li C, Chen J, Xiang D, et al. Predictors of mortality in bloodstream infections caused by multidrug-resistant gram-negative bacteria: 4 years of collection. Am J Infect Control. 2016;45:59–64. https://doi.org/10.1016/j.ajic.2016.08.008.
43. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: Importance of combination therapy. Clin Infect Dis. 2012;55:943–50. https://doi.org/10.1093/cid/cis588.
44. Rihani DS, Wallace MR, Sieger BE, Waite RA, Fox M, Brown SA, et al. Overtreatment of carbapenemase-producing Enterobacteriaceae. Scand J Infect Dis. 2012;44:325–9. https://doi.org/10.3109/00365548.2011.638318.
45. King M, Heil E, Kuriakose S, Bias T, Huang V, El-Beyrouty C, et al. Multicenter study of outcomes with Ceftazidime-Avibactam in patients with Carbapenem-resistant Enterobacteriaceae Infections. Antimicrob Agents Chemother. 2017;61.https://doi.org/10.1128/aac.00449-17.
46. Machuca I, Gutiérrez-Gutiérrez B, Gracia-Ahufinger I, Rivera Espinar F, Cano Á, Guzmán-Puche J, et al. Mortality associated with bacteremia due to colistin-resistant Klebsiella pneumoniae with high-level meropenem resistance: Importance of combination therapy without colistin and carbapenems. Antimicrob Agents Chemother. 2017;61.https://doi.org/10.1128/AAC.00406-17.
47. Lopez-Cortes LE, Cisneros JM, Fernandez-Cuenca F, Bou G, Tomas M, Garnacho-Montero J, et al. Monotherapy versus combination therapy for sepsis due to multidrug-resistant Acinetobacter baumannii: analysis of a multicentre prospective cohort. J Antimicrob Chemother. 2014;69:3119–26. https://doi.org/10.1093/jac/dku233.
48. Ghafur A, Devarajan V, Raja T, Easow J, Raja M, Sreenivas S, et al. Monotherapy versus combination therapy against carbapenem-resistant Gram-negative bacteria: a retrospective observational study. Indian J Cancer. 2017;53:592–4. https://doi.org/10.4103/0019-509X.204767.
49. Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother. 2015;70:2133–43. https://doi.org/10.1093/jac/dkv086.
50. Salah H, Alsamani O. Impact of different antibiotic regimens in the treatment of carbapenem-resistant bacteria on mortality and readmission. Bahrain Med Bullet. 2020;42:250–3 https://www.embase.com/search/results?subaction=viewrecord&id=L2005617415&from=export.
51. Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M, et al. High rate of colistin resistance among patients with carbapenem-resistant Klebsiella pneumoniae infection accounts for an excess of mortality. Clin Microbiol Infect. 2012;19:E23–30. https://doi.org/10.1111/1469-0691.12070.
52. Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F, Pontes-Moreno A, López-Cerero L, Pascual A, et al. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant Klebsiella pneumoniae. J Antimicrob Chemother. 2019;70:905–13. https://doi.org/10.1093/jac/dku432.
53. Tumbarello M, Trecarichi EM, Corona A, De Rosa FG, Bassetti M, Mussini C, et al. Efficacy of Ceftazidime-Avibactam salvage therapy in patients with infections caused by Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae. Clin Infect Dis. 2018;68:355–64. https://doi.org/10.1093/cid/ciy492.
54. Katip W, Uitrakul S, Oberdorfer P. The effectiveness and nephrotoxicity of loading dose colistin combined with or without meropenem for the treatment of carbapenem-resistant A. baumannii. Int J Infect Dis. 2020;97:391–5. https://doi.org/10.1016/j.ijid.2020.05.100.
55. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis. 2017;17:726–34. https://doi.org/10.1016/S1473-3099(17)30228-1.
56. Niu T, Luo Q, Li Y, Zhou Y, Yu W, Xiao Y. Comparison of Tigecycline or Cefoperazone/Sulbactam therapy for bloodstream infection due to Carbapenem-resistant Acinetobacter baumannii. Antimicrob Resist Infect Control. 2019;8:52. https://doi.org/10.1186/s13756-019-0502-x.
57. Katip W, Uitrakul S, Oberdorfer P. A comparison of colistin versus colistin plus meropenem for the treatment of carbapenem-resistant acinetobacter baumannii in critically ill patients: A propensity score-matched analysis. Antibiotics. 2020;9:1–11. https://doi.org/10.3390/antibiotics9100647.
58. Amat T, Gutiérrez-Pizarraya A, Machuca I, Gracia-Ahufinger I, Pérez-Nadales E, Torre-Giménez Á, et al. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant Acinetobacter baumannii. Clin Microbiol Infect. 2017;24:630–4. https://doi.org/10.1016/j.cmi.2017.09.016.
59. Medeiros GS, Rigatto MH, Falci DR, Zavascki AP. Combination therapy with polymyxin B for carbapenemase-producing Klebsiella pneumoniae bloodstream infection. Int J Antimicrob Agents. 2018;53:152–7. https://doi.org/10.1016/j.ijantimicag.2018.10.010.
60. Gomez-Simmonds A, Nelson B, Eiras DP, Loo A, Jenkins SG, Whittier S, et al. Combination regimens for treatment of carbapenem-resistant Klebsiella pneumoniae bloodstream infections. Antimicrob Agents Chemother. 2016;60:3601–7. https://doi.org/10.1128/AAC.03007-15.
61. Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. Epidemiol Infect. 2012;141:1214–22. https://doi.org/10.1017/S095026881200194X.
62. Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzarlis K, Apostolopoulou O, et al. Colistin versus colistin combined with ampicillin-sulbactam for multiresistant Acinetobacter baumannii ventilator-associated pneumonia

treatment: an open-label prospective study. Indian J Crit Care Med. 2018;22:67–77. https://doi.org/10.4103/ijccm.IJCCM_302_17.
63. Shi H, Lee JS, Park SY, Ko Y, Eom JS. Colistin plus Carbapenem versus Colistin monotherapy in the treatment of Carbapenem-resistant Acinetobacter baumannii pneumonia. Infect Drug Resist. 2019;12:3925–34. https://doi.org/10.2147/idr.S234211.
64. Park JJ, Seo YB, Lee J, Choi YK, Jeon J. Colistin monotherapy versus colistin-based combination therapy for treatment of bacteremia in burn patients due to carbapenem-resistant gram negative bacteria. Burns. 2020;46:1848–56. https://doi.org/10.1016/j.burns.2020.06.014.
65. Durante-Mangoni Emanuele, Signoriello Giuseppe, Andini Roberto, Mattei Annunziata, De Cristoforo Maria, Murino Patrizia, et al. Colistin and Rifampicin compared with Colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. Clin Infect Dis. 2013;57:349–58. https://doi.org/10.1093/cid/cit253.
66. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018;18:391–400. https://doi.org/10.1016/S1473-3099(18)30099-9.
67. Yilmaz GR, Guven T, Guner R, Kocak Tufan Z, Izdes S, Tasyaran MA, et al. Colistin alone or combined with sulbactam or carbapenem against A. baumannii in ventilator-associated pneumonia. J Infect Dev Ctries. 2015;9:476–85. https://doi.org/10.3855/jidc.6195.
68. Zhang S, Yang Z, Sun L, Wang Z, Sun L, Xu J, et al. Clinical observation and prognostic analysis of patients with Klebsiella pneumoniae bloodstream infection. Front Cell Infect Microbiol. 2020;10:577244. https://doi.org/10.3389/fcimb.2020.577244.
69. De la Calle C, Rodríguez O, Morata L, Marco F, Cardozo C, García-Vidal C, et al. Clinical characteristics and prognosis of infections caused by OXA-48 carbapenemase-producing Enterobacteriaceae in patients treated with ceftazidime-avibactam. Int J Antimicrob Agents. 2019;53:520–4. https://doi.org/10.1016/j.ijantimicag.2018.11.015.
70. Villegas MV, Pallares CJ, Escandón-Vargas K, Hernández-Gómez C, Correa A, Álvarez C, et al. Characterization and clinical impact of bloodstream infection caused by carbapenemase-producing enterobacteriaceae in seven Latin American countries. PLoS ONE. 2016;11.https://doi.org/10.1371/journal.pone.0154092.
71. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, et al. Ceftazidime-Avibactam is superior to other treatment regimens against Carbapenem-resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother. 2017;61.https://doi.org/10.1128/aac.00883-17.
72. Karaiskos I, Daikos GL, Gkoufa A, Adamis G, Stefos A, Symbardi S, et al. Ceftazidime/avibactam in the era of carbapenemase-producing Klebsiella pneumoniae: experience from a national registry study. J Antimicrob Chemother. 2020;76:775–83. https://doi.org/10.1093/jac/dkaa503.
73. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother. 2014;58:2322–8. https://doi.org/10.1128/AAC.02166-13.
74. Tofas P, Skiada A, Angelopoulou M, Sipsas N, Pavlopoulou I, Tsaousi S, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections in neutropenic patients with haematological malignancies or aplastic anaemia: Analysis of 50 cases. Int J Antimicrob Agents. 2016;47:335–9. https://doi.org/10.1016/j.ijantimicag.2016.01.011.
75. Porwal R, Gopalakrishnan R, Rajesh NJ, Ramasubramanian V. Carbapenem resistant Gram-negative bacteremia in an Indian intensive care unit: A review of the clinical profile and treatment outcome of 50 patients. Indian J Crit Care Med. 2014;18:750–3. https://doi.org/10.4103/0972-5229.144021.
76. Zhou C, Jin L, Wang Q, Wang X, Chen F, Gao Y, et al. Bloodstream infections caused by carbapenem-resistant enterobacterales: risk factors for mortality, antimicrobial therapy and treatment outcomes from a prospective multicenter study. Infect Drug Resist. 2021;14:731–42. https://doi.org/10.2147/IDR.S294282.
77. Tsai WC, Syue LS, Ko WC, Lo CL, Lee NY. Antimicrobial treatment of monomicrobial phenotypic carbapenem-resistant Klebsiella pneumoniae bacteremia: two are better than one. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2021.https://doi.org/10.1016/j.jmii.2021.09.002.
78. Liang CA, Lin YC, Lu PL, Chen HC, Chang HL, Sheu CC. Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant Acinetobacter baumannii. Clin Microbiol Infect. 2017;24:908.e1-.e7. https://doi.org/10.1016/j.cmi.2017.10.033.
79. Chusri S, Singkhamanan K, Wanitsuwan W, Suphasynth Y, Kositpantawong N, Panthuwong S, et al. Adjunctive therapy of intravenous colistin to intravenous tigecycline for adult patients with non-bacteremic post-surgical intra-abdominal infection due to carbapenem-resistant Acinetobacter baumannii. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy. 2019;25:681–6.https://doi.org/10.1016/j.jiac.2019.03.017.
80. Chang K, Wang H, Zhao J, Yang X, Wu B, Sun W, et al. Polymyxin B/Tigecycline combination vs. Polymyxin B or Tigecycline alone for the treatment of hospital-acquired pneumonia caused by Carbapenem-resistant Enterobacteriaceae or Carbapenem-resistant Acinetobacter baumannii. Front Med. 2022;9.https://doi.org/10.3389/fmed.2022.772372.
81. Calò F, Onorato L, De Luca I, Macera M, Monari C, Durante-Mangoni E, et al. Outcome of patients with carbapenem-resistant Acinetobacter baumannii infections treated with cefiderocol: A multicenter observational study. J Infect Public Health. 2023;16:1485–91. https://doi.org/10.1016/j.jiph.2023.06.009.
82. Zha L, Zhang X, Cheng Y, Xu Q, Liu L, Chen S, et al. Intravenous Polymyxin B as adjunctive therapy to high-dose Tigecycline for the treatment of nosocomial pneumonia due to Carbapenem-resistant Acinetobacter baumannii and Klebsiella pneumoniae: a propensity score-matched cohort study. Antibiotics. 2023;12.https://doi.org/10.3390/antibiotics12020273.
83. Katip W, Rayanakorn A, Oberdorfer P, Taruangsri P, Nampuan T, Okonogi S. 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. J Infect Public Health. 2024;17:727–34. https://doi.org/10.1016/j.jiph.2024.03.010.
84. Lin J, Zhang L, Zhou M, Tian X, Chen J, Lu M, et al. Combination therapy of Ceftazidime/Avibactam for the treatment of patients infected with Carbapenem-resistant Klebsiella pneumoniae: a multicenter retrospective study. Infect Dis Ther. 2023;12:2165–77. https://doi.org/10.1007/s40121-023-00852-8.
85. Hao M, Yang Y, Guo Y, Wu S, Hu F, Qin X. Combination regimens with Colistin sulfate versus Colistin sulfate monotherapy in the treatment of infections caused by Carbapenem-resistant gram-negative Bacilli. Antibiotics. 2022;11.https://doi.org/10.3390/antibiotics11101440.
86. Kaye KS, Marchaim D, Thamlikitkul V, Carmeli Y, Chiu C-H, Daikos G, et al. Colistin monotherapy versus combination therapy for Carbapenem-resistant organisms. NEJM Evidence. 2023;2.https://doi.org/10.1056/EVIDoa2200131.
87. Sirijatuphat R, Thawornkaew S, Ruangkriengsin D, Thamlikitkul V. Colistin monotherapy versus Colistin plus Sitafloxacin for therapy of Carbapenem-resistant Acinetobacter baumannii infections: a preliminary study. Antibiotics. 2022;11.https://doi.org/10.3390/antibiotics11121707.
88. Chen J, Lin J, Weng J, Ju Y, Li Y. Clinical success of anti-infective combination therapy compare to monotherapy in patients with carbapenem-resistant Pseudomonas aeruginosa infection: a 10-years retrospective study. BMC Infectious Diseases. 2024;24.https://doi.org/10.1186/s12879-024-09060-2.
89. Li K, Li D, Dong H, Ren D, Gong D, Wang S, et al. Ceftazidime-Avibactam combination therapy versus monotherapy for the treatment Carbapenem-resistant gram-negative bacterial infections: a retrospective observational study. Infect Drug Resist. 2024;17:1281–9. https://doi.org/10.2147/idr.S452805.
90. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Appl Eng Agric. 2002;18(6):727–34. https://doi.org/10.1007/BF01739916.
91. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care mterventtons. J Epidemiol Community Health. 1998;6:377–84. https://doi.org/10.1371/journal.pntd.0008682.
92. Pranita D. Tamma, Heil, EL, Julie Ann Justo, Amy J. Mathers, Michael J. Satlin, Bonomo RA. Infectious Diseases Society of America 2024 Guidance

on the Treatment of Antimicrobial-Resistant Gram-Negative Infections. Clini Infect Dis. 2024.https://doi.org/10.1093/cid/ciae403/7728556.
93. Tamma PD AS, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clinical Infectious Diseases. 2023;Jul 18:ciad428:Epub ahead of print.https://doi.org/10.1093/cid/ciad428
94. Tumbarello M, Viale P, Viscoli C, al. E. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae Carbapenemase–producing K. pneumoniae: importance of combination therapy. Clin Infect Dis. 2012;55.https://doi.org/10.1093/cid/cis588.
95. Paul M, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, L L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia TheCochrane Library. 2003.https://doi.org/10.1002/14651858.CD003038.
96. Nutman A, Lellouche J, Temkin E, Daikos G, Skiada A, Durante-Mangoni E, et al. Colistin plus meropenem for carbapenem-resistant Gram-negative infections: in vitro synergism is not associated with better clinical outcomes. Clin Microbiol Infect. 2020;26:1185–91. https://doi.org/10.1016/j.cmi.2020.03.035.
97. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. BMJ-British Med J. 2004;328:668–72F. https://doi.org/10.1136/bmj.38028.520995.63.
98. Buehrle DJ, Shields RK, Clarke LG, Potoski BA, Clancy CJ, Nguyen MH. Carbapenem-resistant Pseudomonas aeruginosa bacteremia: risk factors for mortality and microbiologic treatment failure. Antimicrob Agents Chemother. 2017;61.https://doi.org/10.1128/aac.01243-16.
99. Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, et al. Clinical outcomes, drug toxicity, and emergence of Ceftazidime-Avibactam Resistance among patients treated for Carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis. 2016;63:1615–8. https://doi.org/10.1093/cid/ciw636.

Publisher's Note