SYSTEMATIC REVIEW

Polymyxin Monotherapy vs. Combination Therapy for the Treatment of Multidrug-resistant Infections: A Systematic Review and Meta-analysis

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Abstract

Objectives: The objective of this review was to compare the effectiveness of Colistin monotherapy and combination therapy for the treatment of multidrug-resistant gram-negative bacterial infections.

Data sources: PubMed, Cochrane Library.

Study eligibility, interventions, and exclusions: In this systematic review, we included all retrospective and prospective studies and randomized controlled trials (RCTs) that compared intravenous polymyxin monotherapy and combination therapy with any other antibiotic for treating multidrug-resistant infections. Studies using inhaled polymyxins with 5 or less than 5 patients were excluded. The primary outcome was 30-day all-cause mortality and if not reported at day 30 we extracted and documented the closest time point. Both crude outcome rates and adjusted effect estimates were extracted for mortality.

Study appraisal, data extraction and synthesis: Search string used was "(Colistin OR polymyxin) AND (*Enterobacteriaceae* OR *Klebsiella* OR *Acinetobacter* OR *Escherichia coli* OR *Pseudomonas*) AND (random OR prospective OR retrospective OR cohort OR observational OR blind)." Thirty-nine studies were included in our analysis; out of which 6 RCTs were included and 9 studies used carbapenem as the adjunctive antibiotic. Each study was screened and reviewed for eligibility independently by two authors and data extrapolated on an Excel sheet.

Results: The meta-analysis of polymyxin monotherapy vs. combination therapy in multidrug-resistant infections yielded an odds ratio (OR) of 0.81 (95% confidence interval [CI]: 0.65–1.01) with minimal heterogeneity ($I^2 = 40\%$), whereas pooled analysis of this comparison in studies that included carbapenem as combination therapy yielded an OR of 0.64 (CI: 0.40–1.03; $I^2 = 62\%$). Likewise, the pooled analysis of the RCTs yielded an OR of 0.82 (95% CI: 0.58–1.16, $I^2 = 22\%$). All these showed no statistical significance. However, it was seen that polymyxin combination therapy was more effective in multidrug-resistant infections compared to polymyxin monotherapy. The effectiveness was more glaring when carbapenems were used as the combination drug instead of any other antibiotic and more so in many *in vitro* studies that used polymyxin combination therapy.

Conclusion: Although statistically insignificant, it would be prudent to use polymyxin combination therapy to treat multidrug-resistant gram-negative bacilli (GNB) infection over monotherapy with preference to use carbapenem as the adjunct alongside polymyxins.

Keywords: Carbapenems, Colistin, Combination therapy, Gram-negative bacilli infections, Monotherapy, Multidrug resistant (MDR), Polymyxin B.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23720

Introduction

Polymyxin E (Colistin) was originally isolated in 1947 from soil bacterium *Paenibacillus polymyxa* subsp. *colistinus*.[1] Polymyxin B and colistin belong to the class of polymyxins, which is a polypeptide group of antibiotics. Polymyxins share their structure with cationic antimicrobial peptides (CAMPs) like defensins and gramicidins.[2] CAMPs represent the first line of defense against bacterial infections. Polymyxins are cationic polypeptides that consist of a cyclic heptapeptide possessing a tripeptide side chain acylated at the N-terminus by a fatty acid tail.[3,4] N-terminal fatty acyl segment is hydrophobic and is associated with both toxicity and the antimicrobial property.[5,6] Colistin and polymyxin B differ by only a single amino acid in the peptide ring with phenylalanine in polymyxin B and leucine in Colistin.[7] Polymyxin B is administered directly as an active antibiotic, whereas Colistin is administered as an inactive prodrug, colistin methanesulfonate (also known as colistimethate [CMS]).[7] Colistimethate is formed by the reaction of colistin with formaldehyde and sodium bisulfite.[8] This prodrug is transformed in aqueous media and also *in vivo* in biological fluids and is converted into colistin and several inactive methanesulfonated compounds.[9,10]

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How to cite this article: Samal S, Mishra SB, Patra SK, Rath A, Dash A, Nayak B, *et al*. Polymyxin Monotherapy vs. Combination Therapy for the Treatment of Multidrug-resistant Infections: A Systematic Review and Meta-analysis. Indian J Crit Care Med 2021;25(2):199–206.

Source of support: Nil

Conflict of interest: None

Mechanism of Action

The outer membrane of gram-negative bacteria is the target for polymyxins. Because of an electrostatic interaction occurring between the -diaminobutyric acid (Dab) residue of the positively charged polymyxin on one side and the phosphate groups of the negatively charged lipid A membrane on the other side, divalent

cations (Ca^{2+} and Mg^{2+}) are displaced from the negatively charged phosphate groups of membrane lipids.[11] The lipopolysaccharide (LPS) is therefore destabilized consequently increasing the permeability of the bacterial membrane leading to leakage of the cytoplasmic content and ultimately causing cell death.[4,12] The endotoxin of gram-negative pathogens corresponds to the lipid A portion of the LPS; polymyxins have the ability to bind to and neutralize this LPS molecule released during cell lysis.[13] Inhibition of vital respiratory enzymes (inhibition of type II nicotinamide adenine dinucleotide–quinone oxidoreductases [NDH-2]) in the bacterial inner membrane is another proposed mechanism of action.[14] Even though the LPS is the initial target, the exact mode of action of polymyxins still remains uncertain.

Spectrum of Activity

Polymyxins have a narrow antibacterial spectrum including most members of the *Enterobacteriaceae* and common nonfermentative gram-negative bacteria including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*.[12]

Proteus spp., *Morganella morganii*, *Providencia* spp., *Serratia marcescens*, *Pseudomonas mallei*, *Burkholderia cepacia*, *Chromobacterium* spp., *Edwardsiella* spp., *Brucella*, *Legionella*, *Campylobacter*, and *Vibrio cholerae* are intrinsically resistant to the drug. Gram-negative cocci (*Neisseria* spp.), gram-positive bacteria, and anaerobic bacteria are not covered by polymyxins.[12]

Rationale

Zusman et al. conducted a meta-analysis to look into the *in vitro* studies of synergism between polymyxin and other antibiotics.[15] High synergism (up to 75%) is seen between polymyxins and carbapenems against *A. baumannii* strains. The combination therapy increased the bactericidal property of *A. baumannii* from 24 to 75%. Synergy was higher with meropenem and doripenem compared to imipenem for *A. baumannii*. Carbapenem-resistant, Colistin-susceptible *A. baumannii* showed a synergy rate of 71%. For *Klebsiella pneumoniae,* 44% synergism was seen. Doripenem showed higher synergism in comparison with imipenem and meropenem. Carbapenem-resistant, Colistin-susceptible *K. pneumoniae* showed a synergy rate of 55%. *P. aeruginosa* showed a synergy rate of 50%. So, overall, *in vitro* studies showed synergy between carbapenems and polymyxins.

We planned to do a systematic meta-analysis of all the clinical trials to date.

Objective

We sought to examine the effectiveness of polymyxin-based combination vs. monotherapy by antibiotic types and bacterial species.

Methods

Protocol

Our protocol was inspired by the meta-analysis and systematic review by Zusman et al. (J Antimicrob Chemother, DOI: 10.1093/jac/dkw377).[15]

Eligibility Criteria

We included all clinical studies [whether retrospective, prospective or RCTs] comparing intravenous polymyxin (Colistin or polymyxin B) monotherapy vs. any polymyxin-based combination therapy in adult patients with documented infection caused by polymyxin-susceptible, carbapenem-resistant (CR) or carbapenemase-producing GNB provided that the study reported on the outcomes for a specific polymyxin and a specific combination regimen (named antibiotics). If more than one comparison was reported, we included all reported comparisons. No language or year restrictions were applied. We did not include studies using inhaled polymyxins. Only studies reporting on more than 5 patients per treatment group were included.

Information Sources

We searched PubMed, the Cochrane Library, references of all included studies, and narrative or systematic reviews on the topic.

Search

In the databases, we used the following search string: "(Colistin OR polymyxin) AND (*Enterobacteriaceae* OR *Klebsiella* OR *Acinetobacter* OR *E. coli* OR *Pseudomonas*) AND (random OR prospective OR retrospective OR cohort OR observational OR blind)." We estimated that this search string will be relatively sensitive. The last search was run on December 31, 2018.

Study Selection

Any study from our search that compared Colistin or polymyxin in combination against being used alone for treating intensive care unit (ICU)-acquired infections were considered provided the number of subjects included were more than 5. Studies that used inhaled Colistin were excluded.

Data Collection Process and Data Items

Each study was screened and reviewed for eligibility independently by two authors. In case of missing data for an eligible study, an attempt was made to contact the study authors for clarification. Data were tabulated in an Excel sheet. The primary outcome was 30-day all-cause mortality and if not reported at day 30 we extracted and documented the closest time point. Both crude outcome rates and adjusted effect estimates were extracted for mortality. Data were extracted independently by two authors using a predefined data extraction form and then compared for verification. In the event of a dispute, a third author acted as a referee. From individual studies, we sought to extract patient demographics, formulation and dosage including loading for polymyxins and the combination antibiotic, clinical data regarding the infection including source, place of acquisition of sepsis presentation and severity, and types and resistance profile of the bacteria.

Synthesis of Results

Data in the Excel sheet were analyzed and evaluated using RevMan 5.3.

Additional Analysis

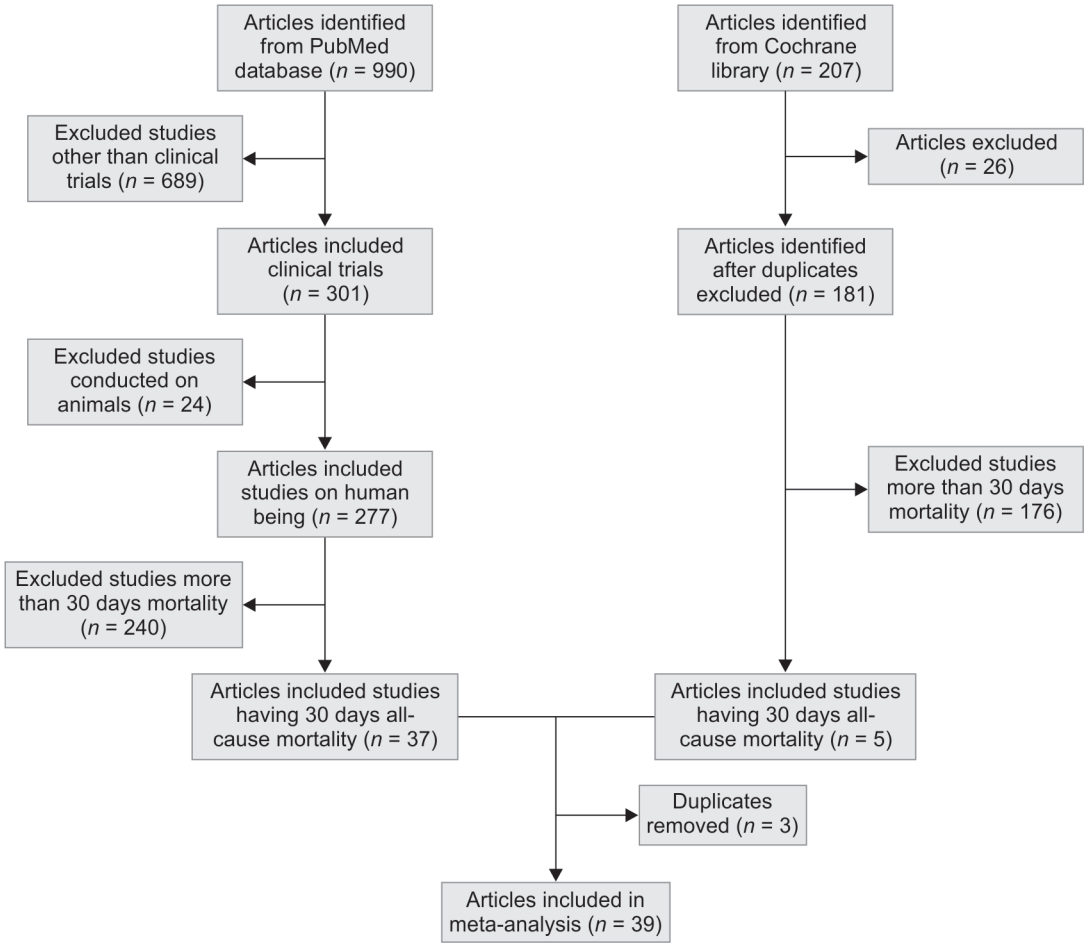
RCTs were studied separately and a separate analysis was done for them.

Results

Study Selection

Using the search key mentioned above within the stipulated time period, 990 articles were identified from PubMed database, whereas 207 were identified from the Cochrane Library. After removing duplicates, animal studies, and studies with more

Flowchart 1: PRISMA flowchart/study selection



than 30-day mortality rate, 39 clinical trials finally qualifying our criteria were considered. Only studies that were clinical trials were considered (Flowchart 1).

Out of the 39 studies that were selected for this meta-analysis, the majority of the studies were conducted in Europe (Greece, Turkey, Spain, and Italy).[16–43] Five of them were conducted in America,[44–48] Asia[49–53], and 1 in Africa (Egypt).[54] Seventeen of the studies were prospective studies,[16,18–20,25–29,31,39,41,42,47,54] whereas 22 were retrospective studies. In total, there were 6 RCTs. Sixteen of the 39 studied the effect of Colistin or another drug or in combination on *A. baumannii*,[18,19,24,25,27,30,35,38,40,41,43,48–51,53] 11 studied the effect of therapy on *K. pneumoniae*,[16,17,20,21,26,28,31,37,39,46,54] 2 studies dealt with the role of therapy in *P. aeruginosa*[34,48], and the rest dealt with any kind of sepsis/infection in ICU or polymicrobial infection.[22,23,29,32,33,36,42,44,45,47,52] Twenty-seven studies were conducted solely in the ICU setup[18–24,26–28,30–32,37,38,41–45,48–54], whereas the rest of the studies included patients from any setup (ward/high dependency unit/ICU) with the infections being treated with Colistin or combination therapy. Nine of these 39 focused on bloodstream infections alone[17,20,21,28,29,39,40,46,51], 2 on pneumonia[30,45], 6 on ventilator-associated pneumonia[18,38,41,43,53,54], 4 on mixed or multiple-site infections[27,31–33] and the rest took any site of infection into account. All of these studies except 2 studied the effect of Colistin as compared to combination therapy. Polymyxin B was the antibiotic studied in the other 2.[47,48] Carbapenems and tigecycline were the most used antibiotics for combination therapy followed by aminoglycosides, rifampicin, and beta-lactam plus beta-lactamase inhibitor. Fosfomycin and vancomycin were used in 1 study each.

All-cause Mortality in Combination vs. Monotherapy

All 39 studies were analyzed. In total, 4863 patients were included in the analysis. The meta-analysis yielded an OR of 0.81 with CI from 0.65 to 1.01. This had a *p*-value of 0.06. Heterogeneity measured I^2 was 26% (Fig. 2). We did a separate meta-analysis of only the RCTs. Six studies were analyzed and yielded an OR of 0.82 with a CI of 0.58–1.16. This was not statistically significant. The heterogeneity was $I^2 = 22$ (Fig. 3). We also did an analysis including those studies, which had only carbapenems as a combination. Nine studies were analyzed and yielded an OR of 0.64 with a CI of 0.40–1.03. This was not statistically significant. The heterogeneity was $I^2 = 62$ (Fig. 1).

Discussion

Klebsiella and *Acinetobacter* are the commonest organisms found in ICUs with very high resistance to antibiotics. The newer strains isolated in most of the studies were resistant to carbapenems in most of the cases.[54] Targeting these organisms with a multifaceted

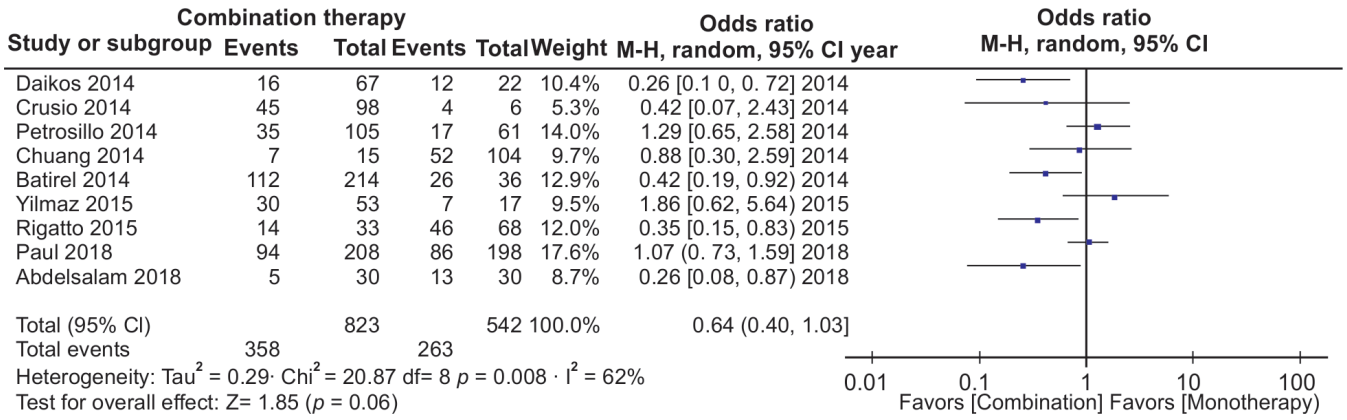


Fig. 1: All-cause mortality in studies where carbapenems were used in combination therapy

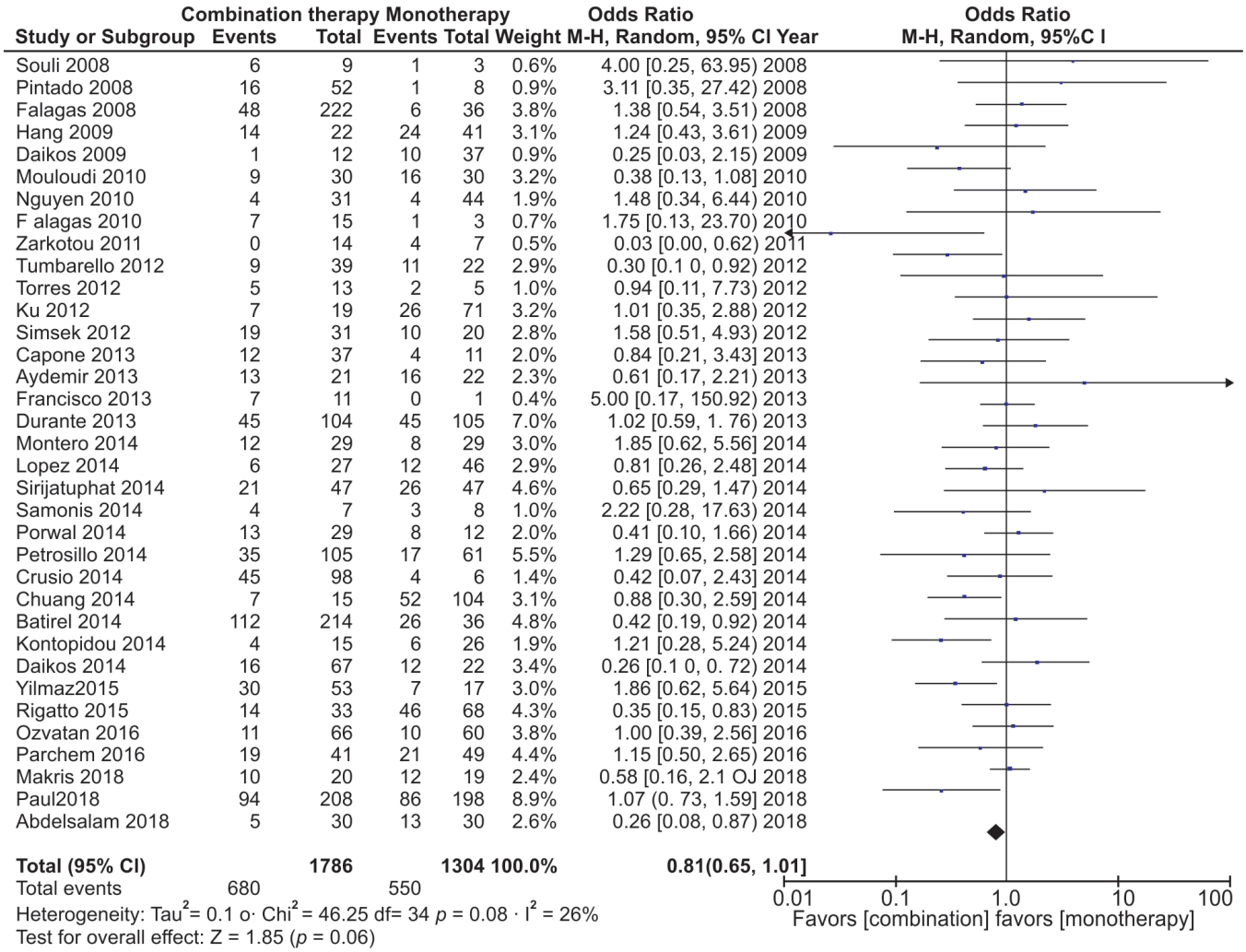


Fig. 2: All-cause mortality in all included studies

approach seems to be a way out. Various combinations of antibiotics have been used to treat these multidrug-resistant infections in the hope to achieve results *in vivo* where *in vitro* tests have deemed the infections to be untreatable.

We made an attempt to compile the evidence available to date on the use of combination therapy with polymyxins in comparison to monotherapy with polymyxins. These 39 studies were found which had comparative groups of monotherapy in comparison to

Table 1: Comparison of RCTs

Sl. No.	*Author*	*Year*	*Location*	*Organism*	*Setting*	*Infection type*	*Polymyxin*	*Combination*	*No. of Pt.*	*Mortality*
1	Aydemir et al.[18]	2013	Turkey	CR-AB	ICU	VAP	Colistin	Rifampin	43	No difference in mortality or clinical, laboratory or microbiological clearance Significant reduction in time to microbiological clearance in combination arm
2	Durante-Mangoni et al.[19]	2013	Italy	XDR-AB	ICU	Any	Colistin	Rifampin	210	No mortality benefit, but better bacteriological clearance
3	Sirijatuphat et al.[49]	2014	Thailand	CR-AB	ICU	Any	Colistin	Fosfomycin	94	More favorable microbiological response significantly Trend of lower 28-day all-cause mortality levels
4	Abdelsalam et al.[54]	2018	Egypt	MDR KP	ICU	VAP	Colistin	Meropenem	60	Combination group showed a significant decrease in mortality
5	Makris et al.[41]	2018	Greece	MDRAB	ICU	VAP	Colistin	Ampicillin sulbactam	39	Multiple regression analysis—combination therapy was an independent predictor of good clinical response
6	Paul et al.[42]	2018	Greece	Any	ICU	Any	Colistin	Meropenem	406	No overall mortality benefit. Benefit only against *Klebsiella pneumoniae* infections, (not adequately powered)

CR, carbapenem resistant; AB, *Acinetobacter baumannii;* ICU, intensive care unit; VAP, ventilator-acquired pneumonia; XDR, extremely drug resistant; MDR, multidrug resistant

combination therapy which had mortality as an outcome. We did not assess the clinical clearance of the organisms as there is always a very high risk of bias associated with such outcomes, both in terms of definition as well as data collection.

The *in vitro* studies have shown that there is a synergism between carbapenems and polymyxins.[15] This is seen predominantly in *Acinetobacter* strains. *Klebsiella* and *Pseudomonas* also show synergism in up to 50% of strains. The clinical trials though are very varied. Various combinations have been tried. The most common agent that has been used in combination with Colistin/polymyxin B is the tigecycline. We did a subgroup analysis of the studies that included only carbapenems as combination therapy. It showed a significant improvement in all-cause mortality. Though the largest RCT did not find any benefit, this finding may be a hypothesis for future trials.[42]

The overall analysis showed lesser mortality with combination therapy, though it was not statistically significant. This was consistent if we included all the studies or if we looked only at the RCT. This finding is consistent with previous meta-analyses and trials. Thirty-three studies were observational in nature. The major risk of bias in these studies is the classification bias which means the authenticity that the patient in the said group actually received that therapy or not. There was a high risk of bias as there were no clear definitions. The other major problem with observational studies is the selection bias. In some studies, some patients were given monotherapy as they were selected because of less severe infection or an easily treatable source of infection, e.g., urinary tract infections. Most of the studies do not report on the minimum inhibitory concentration (MIC) values for carbapenems. Only the study by Navarro–San Francisco has mentioned about the MIC.[29]

In the 6 RCTs included, almost all showed a trend towards lower mortality in patients receiving combination therapy; however, only the RCT by Abdelsalam et al. found a significant difference in mortality.[54] The largest RCT by Paul et al. showed significant results in case of infections with *K. pneumoniae*, though not adequately powered for it.[42] Two of the RCTs had a very small sample size whose results could not be extrapolated to larger populations.[18,41] Though nearly all of the studies did not find the benefit of the combination therapy, they, however, did show a better bacteriological clearance in patients receiving combination therapy.[19,41,49,54] The higher mortality in patients was attributed to the higher acute physiology and chronic health evaluation (APACHE) II score at admission and higher age. In one of the RCTs, no significant difference in microbiological clearance was found, but the time to the clearance was significantly shorter in patients who received combination therapy.[18] Multiple regression analysis in a study found that combination therapy was an independent predictor of good clinical response.[41]

Our meta-analysis shows that there is a trend towards mortality benefits with combination therapy. This trend is more pronounced when carbapenem is the antibiotic used for combination therapy. This is supported by *in vitro* trials and meta-analysis which support the synergism of combination between polymyxins and carbapenems. This is also supported theoretically by the fact that polymyxins are bacteriostatic agents and maybe a combination will help in more penetration into the bacterial cells and enhance the tidal properties of the carbapenems.

Limitations

The limitations of our study originate from the studies that were included in this analysis. Since most of the studies are observational,

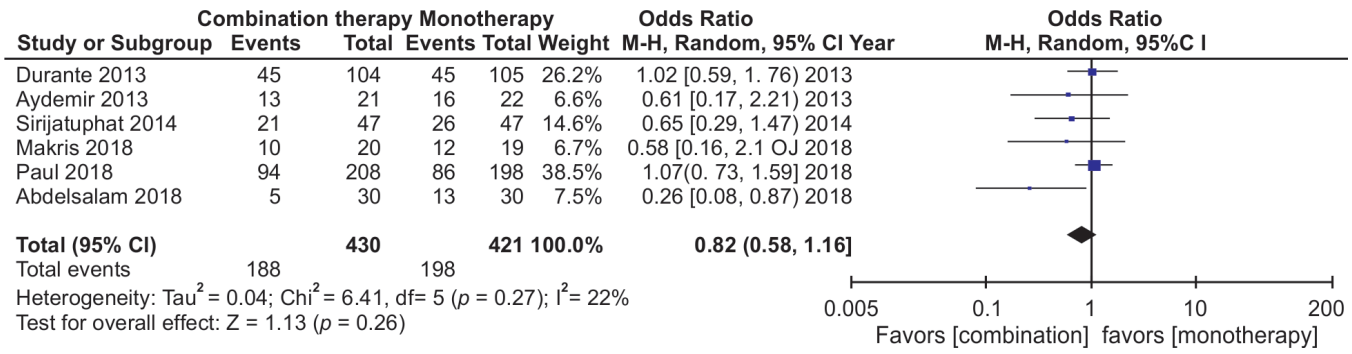


Fig. 3: All-cause mortality in RCTs

they suffer from the shortcomings associated with these trials as explained before. The study endpoint was not mortality in many of the studies. The methodological flaws in the included trial affect this study as well. The *in vitro* evidence is there for carbapenem combination therapy, but it has been evaluated in limited trials. Only 2 RCTs have looked into this combination therapy.[42,54] Though there were a few other studies who did use carbapenems or meropenem, this was not the only adjunctive antibiotic used in these studies.[21–23,26,27,29,38,39,48] Either tigecycline, tetracycline, aminoglycoside or sulbactam was also studied along with carbapenems/meropenem as an adjunct to Colistin. These other antibiotics are not supported by *in vitro* trials. The largest RCT looked at an invalidated composite outcome in a mixed bacterial population.[42] They also reported a reduced renal complication in combination group, which currently we do not have any physiological basis for but something worth looking at in the future.

Risk of Bias

Risk of bias was present in some of the studies, the most prominent being the selection bias as clinicians were not blinded in some.

Conclusion

The use of combination therapy with polymyxin in comparison to monotherapy with polymyxin in a gram-negative infection may show benefits. The combination with a carbapenem especially meropenem is preferred. We need larger RCTs with specific bacterial infection groups to find more conclusive evidence.

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