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Optimal dosing interval of intravenous Colistin monotherapy versus combination therapy: A systematic review and meta-analysis

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Abstract

We aimed to maximize the clinical response and effectiveness of colistin antibiotics in patients with multi-drug (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria, there is an increasing interest in colistin combination therapy with other antibiotics and extended interval dosing regimens. This systematic review and meta-analysis aim is to evaluate if the combination therapy is superior to monotherapy with colistin regarding increased survival and also which dose interval is the most effective to utilize. English language, peer-reviewed journal publications from the first date available to 25 January 2022 were identified by searching the PubMed and Web of Science databases. Forest plots for overall and subgroups and funnel plots were graphed. 42 studies were included in the study. Among them, 38 studies were on combination therapy, and four on dose interval. The overall pooled odds ratio is 0.77 (CI: 0.62; 0.95) (p value < 0.017). The I^2 value was 43% (p value < 0.01). The Begg correlation test of funnel plot asymmetry showed no significant publication bias (0.064). The overall pooled odds ratio for Carbapenem is 0.74 (CI: 0.48; 1.13). A prospective randomized controlled trials (RCT) on 40 adults intensive care unit (ICU) patients with ventilator-associated pneumonia (VAP), comparing the mortality and ICU length of stay of 8- or 24- hour intervals regimens, showed that the ICU length of stay and ICU mortality were; 31.31, 35.3 days, and 32.06, 22.2% in groups 24-h interval and 8- hour interval (p value: 0.39, 0.87), respectively. It seems that combination therapy is associated with drug synergism and increased survival. The extended interval colistin administration may result in higher peak concentration and bacterial eradication. In both cases, we face a dearth of literature.

Key Words: Colistin; carbapenem; combination therapy; dosing interval.

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Colistin (polymyxin E) is recognized as the last line treatment for emerging infections due to multi-drug (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria.[1] The use of colistin was limited in the late 1980s due to its nephrotoxicity and neurotoxicity. However, colistin has increasingly been used as salvage therapy in recent years to treat severe infections in critically ill patients. The limited use of colistin as the last line treatment is the reason for its retained antibacterial effect against MDR/XDR Gram-negative bacilli.[2] Colistin is a multicomponent polypeptide antibiotic, which is composed mainly of colistin A and colistin B.[2] Colistin exerts its effect by targeting the outer membrane of gram-negative bacteria.[1] Colistin is administered in the form of an inactive pro-drug, called colistimethate sodium (CMS) which presents different pharmacokinetic properties from the active drug.[3]

To maximize the clinical response and effectiveness, there is an increasing interest in colistin combination therapy with other antibiotics. However, there is an existent controversy in this regard, and there are concerns about the issue of increased nephrotoxicity. On the other hand, in case of severe infection with MDR and XDR gram-negative bacteria in clinically very ill patients, some clinicians prefer combination therapy. Moreover, combination therapy may be more efficient in case of infection with hetero-resistance gram-

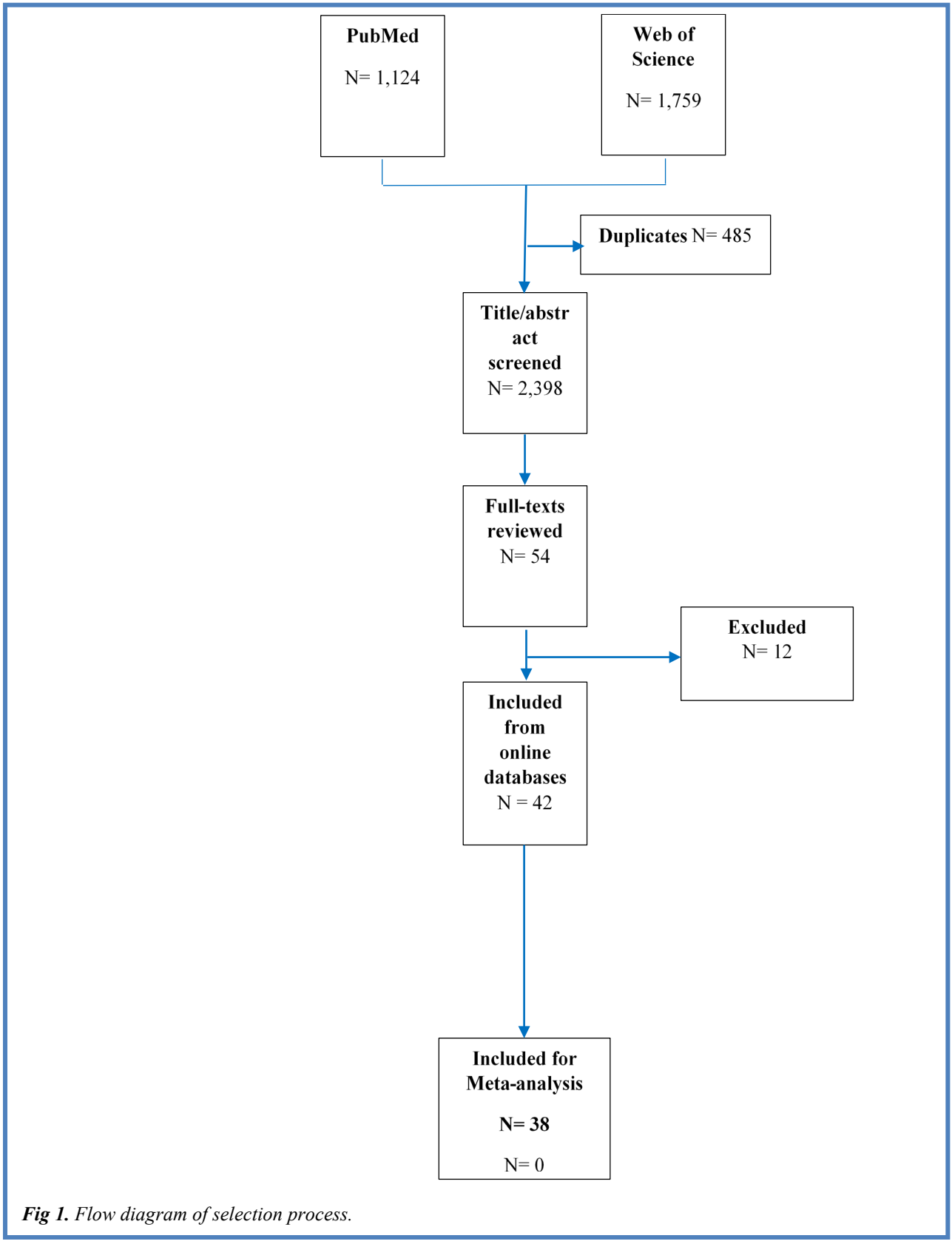

Fig 1. *Flow diagram of selection process.*

negative bacteria.[4] The type of antibiotic that can be used in combination with colistin is also of interest to the medical community. Another existent controversy is regarding the dosing interval of the colistin administration and the optimal dosing interval that maximizes antibacterial activity and minimizes the

nephrotoxicity and emergence of resistance. At present, 8-, 12-, and 24-hourly dosing intervals of colistin are used in patients without renal dysfunction.[5] This systematic review and meta-analysis aim to evaluate if the combination therapy is superior to monotherapy with colistin regarding increased survival and also which dose interval is the safest and most effective.

Materials and Methods

We conducted a systematic review of the evidence for the effect of combination therapy compared to monotherapy of colistin and also the most efficient dosing interval for the colistin administration. English language, peer-reviewed journal publications from the first date available to 25 January 2022 were identified by searching the PubMed and Web of Science databases.[1-50] The various combinations of the following search terms were used: polymyxin, colistin, colistimethate sodium, combination, monotherapy, synergism, dosing interval, frequency. After removing duplicates, the retrieved records were screened for title and abstract. The eligible studies were selected for full-text review and screening. The data of interest were extracted from the studies which did not meet any exclusion criteria. The targeted outcomes were: i) the pooled odds ratio (OR) or risk ratio (RR) to examine the effect of combination therapy compared to monotherapy on survival of the patients; ii) which antibiotic was used

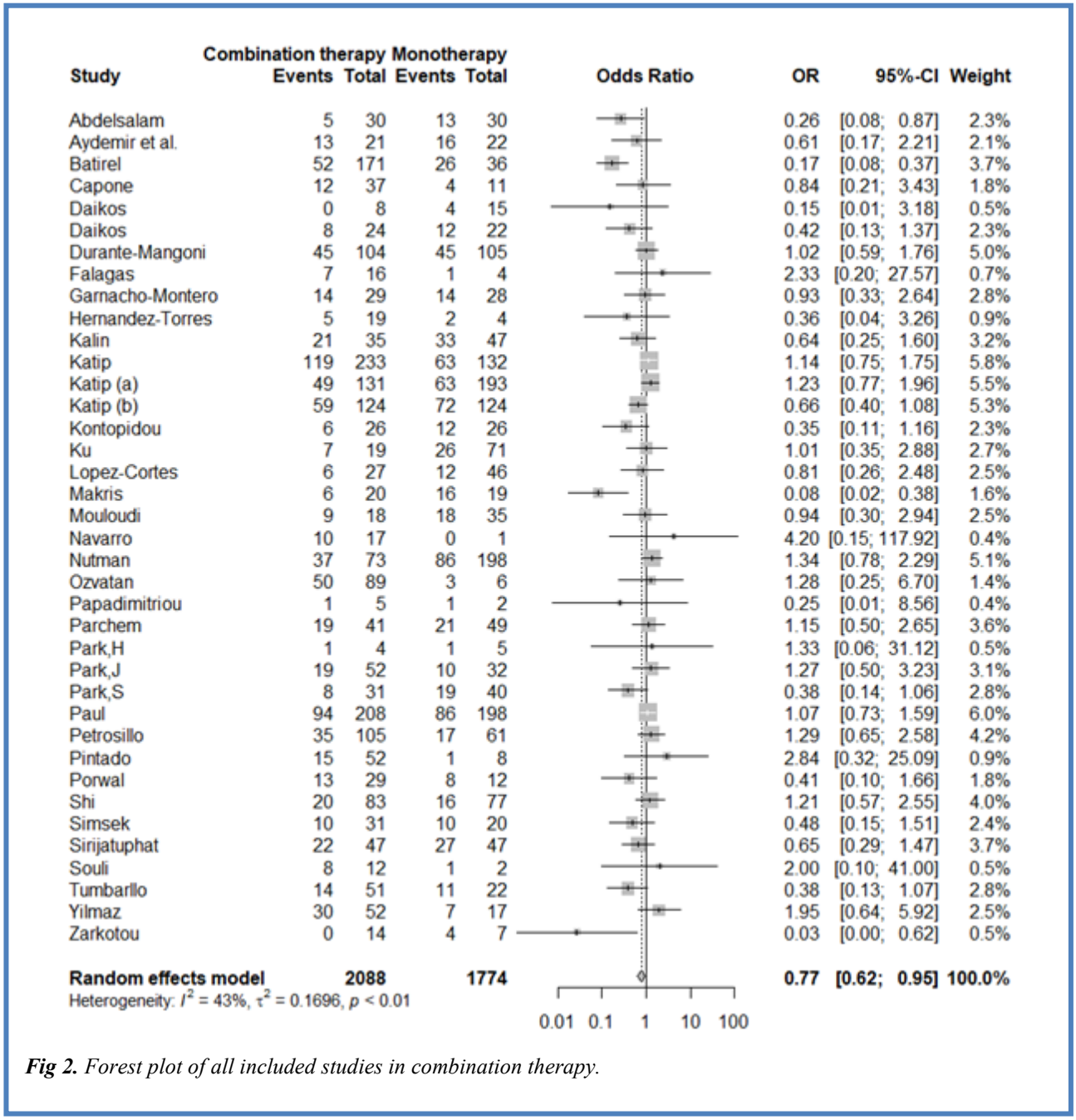

Fig 2. *Forest plot of all included studies in combination therapy.*

for combination therapy; iii) the infection type, and the organism responsible for the infection. The eligible studies were Observational studies (cross-sectional and cohort studies) and randomized clinical trials comparing intravenous colistin monotherapy vs. any colistin-based combination therapy in adult patients with documented infection caused by colistin-susceptible gram-negative bacteria. We excluded the studies that have one or more of the following criteria: 1) studies which were on polymyxin B; 2) systematic review, meta-analysis, grey literature, 3) Studies with no control group, 4) studies that number of patients and mortality are not stratified into combination and monotherapy group; 5) full text in any language other than English. We used a meta package in the R statistical software (version 4.1.1). The OR of mortality following combination therapy was calculated with a 95% confidence interval (CI) for all studies. Mantel-Haenszel Method was used to estimate the pooled OR. The random-effects model was used for calculating pooled OR.

In this study, subgroup analysis was used to report pooled OR for different antibiotics used for combination therapy. The forest plot was used to graphically represent the result of calculated OR for individual studies and conducted subgroup and overall meta-analysis. The I2 statistic was used to evaluate the heterogeneity in the included studies for each subgroup and totally.

A Funnel plot was used to examine the publication bias in studies. The I2 value represents the percentage of total variation among studies due to heterogeneity.

The funnel plot was used to assess the publication bias. Observing any asymmetry visually in the funnel plot was considered as a publication bias. Begg rank correlation method for funnel plot asymmetry was conducted to quantitatively test publication bias.

Results

The flow diagram of selected studies is shown in Figure 1. After removing duplicate records, titles and abstracts of 2,398 studies retrieved from online databases were screened based on title and, or abstract. Fifty-four studies accomplished the inclusion criteria for full-text review. Twelve studies were excluded leading to a final inclusion of 42 studies. The characteristics of the selected studies are shown in ***Table 1 of Supplementary Materials***. Among them, 38 studies were on combination therapy, and four studies were on dose interval, and 38 studies were used for meta-analysis. Thirty-five studies were included in our study consisting of 2088 total cases, 1774 monotherapy patients, and 3862 combination therapy overall.

Combination Therapy

As Figure 2 shows, the overall pooled odds ratio is 0.77 (CI: 0.62; 0.95), which suggests that the odds of all-cause mortality in combination therapy was 23% lower than monotherapy patients (p value < 0.017). The I^2 value was 43% (p value < 0.01), which shows that included studies are heterogeneous.

The evidence of publication bias was tested by visual examination of funnel plot symmetry (Figure 3). There Begg correlation test of funnel plot asymmetry showed that there is no significant publication bias (0.064). The subgroup analysis showed that the overall pooled odds ratio for Aminoglycoside antibiotic is 0.25 (CI: 0.09; 0.72), which means that the odds of all-cause mortality in colistin with Aminoglycoside therapy was 75% lower than monotherapy patients.

The overall pooled odds ratio for Carbapenem and Gentamicin antibiotic is 0.74 (CI: 0.48; 1.13) and 0.89 (CI: 0.32; 2.48), respectively, which statistically is non-significant. The overall pooled odds ratio for Rifampin antibiotic is 0.95 (CI: 0.58, 1.56), which statistically is non-significant. The overall pooled odds ratio for Sulbactam, Tigecycline and Vancomycin antibiotic is 0.68 (CI: 0.14; 3.41), 0.78 (CI: 0.39; 1.53) and 1.11 (CI: 0.75; 1.65) respectively, which statistically is non-significant.

Dosing interval

Four studies were found comparing the different dosing intervals on bacterial eradication, survival, the emergence of resistant strains and, serum concentration of colistin. One of the studies was in vitro setting and compared three dosing intervals regimens (8-, 12- and 24- hourly) on antimicrobial activity against P. aeruginosa and emergence of resistance strain were evaluated. The other was in vivo and clinical settings. This study showed no significant difference between 8-, 12- or 24-hour intervals in overall bacterial kill when the recommended maximum daily dose was administered. However, the eight hourly regimens showed the best efficacy at minimizing the emergence of resistant strains.[6] Ghazaeian et al. (2017)[7] conducted a prospective RCT on 40 adult's ICU patients with ventilator-associated pneumonia (VAP), comparing the mortality and ICU length of stay of 8- or 24- hour intervals regimens. The ICU length of stay and ICU mortality were; 31.31, 35.3 days, and 32.06, 22.2% in groups 24-h interval and 8- hour interval (p value: 0.39, 0.87), respectively. There was not any significant difference in mortality and length of stay between the two groups, which received the maximum recommended dose of colistimethate sodium (CMS) with two different intervals of every 8 or 24 h.[7] Another study was a case report by Luque et al. (2013)[8] on pharmacokinetic/ pharmacodynamic of incremental doses of CMS in the, a critically ill patient infected by an MDR A. baumannii. It was shown that an extended-interval colistin regimen increased the exposure of CMS and colistin and allows a clinical and microbiological optimal response without evidence of toxicity.[8] A study conducted by Daikos et al. (2010)[9] on 13 patients infected with *P. aeruginosa* showed that 8- and 12-hourly regimens do not provide the most effective

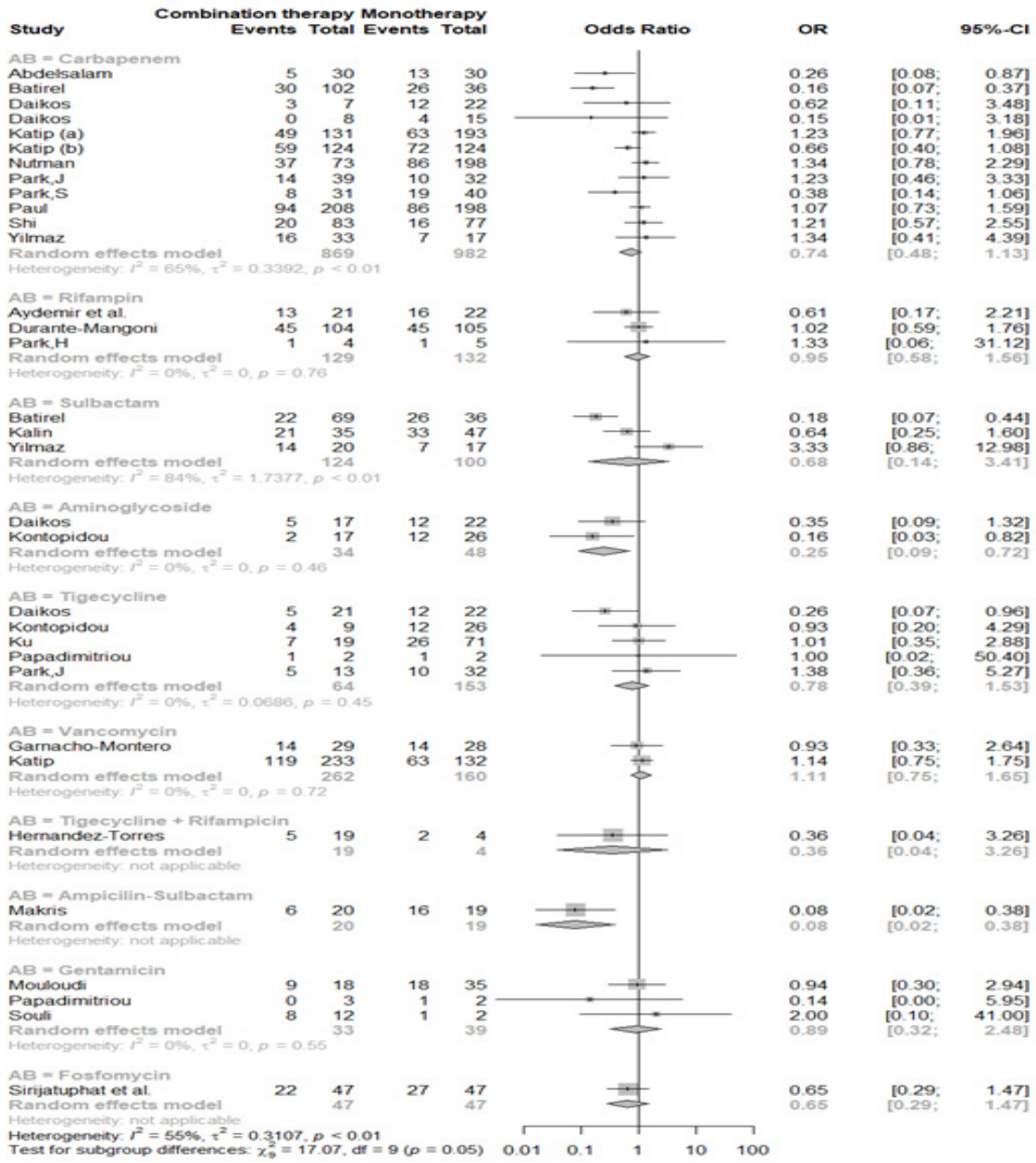

Fig 3. *Forest plot of all included studies in combination therapy.*

serum concentration of Colistin and bacterial eradication and justify administering larger dosages in longer intervals.

Discussion

Our systematic review and meta-analysis showed that combination therapy with colistin as the primary drug significantly decreases the odds of mortality by 23% compared to monotherapy. Various antibiotics have been used in combination with colistin to treat infection with multi-drug resistant gram-negative bacteria. Carbapenem (specifically Meropenem) and Tigecycline are the most used antibiotics in previous studies. The odds of reducing mortality by combination therapy with Carbapenem and Tigecycline are 26% and 22%, respectively. However, the observed decrease in mortality by these two antibiotics is non-significant.

The in vitro studies such as Zusman et al., (2017)[48] suggest a synergism between colistin and Carbapenem, especially in Acinetobacter strains. Up to 50% of Klebsiella and Pseudomonas strains also show synergism. The mechanism suggested for this synergism is that the colistin molecule changes the permeability of bacterial cells, which allows Meropenem to enter the bacterial cell in higher amounts than administering meropenem alone. This combination could even reduce

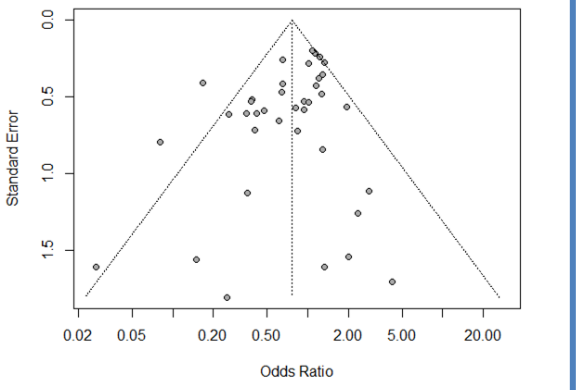

Fig 4. *Funnel plot of included studies.*

the effect of resistance mechanisms.[41] However, in clinical settings, the results are various, and some studies have failed to support that the superiority of colistin plus meropenem over monotherapy. Our meta-analysis also did not show any significant superiority. An explanation for this result is that, in a severe cases of infections, it is more likely to administer the combination therapy rather than monotherapy, particularly in observational studies. In other words, the combination group had a significantly higher proportion of severe cases, and physicians chose combination therapy in more severe cases. Thus, if more severe cases included in the combination group had the same mortality as the monotherapy group, there is a possibility that combination therapy has better efficacy.[41] Tigecycline is a member of the glycylcycline class of antibiotics developed to treat multidrug-resistant gram-positive and gram-negative bacteria and acts as a bacteriostatic antibiotic.[49] Previous studies have shown a synergism between Tigecycline and Colistin in the high dosage of Tigecycline but not in the low dosage of Tigecycline.[50] However, again in clinical setting, Tigecycline plus Colistin combination therapy was not associated with decreased mortality. Like the meropenem case, Tigecycline plus Colistin is used in severe cases. These results highlight a need for matched randomized clinical trials to assess the effect of combination therapy on survival rate. At present, the recommended dosing intervals of colistin are 8-, 12-, and 24-hourly in patients without renal dysfunction. The dosing interval can affect the efficacy of the treatment, side effects of the colistin, and emerging resistant strains. Theoretically, the long half-life of colistin suggests that it could be used in extended intervals, which could result in higher peak concentration and better efficacy, more effective bacterial eradication, and lower side effects and nephrotoxicity.[9] However, an in vitro study showed that extended intervals are associated with the emergence of resistant strains because of periods of low colistin concentration, and there is no significant difference regarding bacterial eradication between different dosing intervals.[6] Another study in a clinical setting showed that there is no difference in survival and efficacy between 8- and 24-hour intervals.[7] There is a dearth of literature in randomized, controlled, clinical trials evaluating the efficacy and safety of once-, twice- and thrice-daily colistin dosing.

Our systematic review and meta-analysis are the first to investigate the efficacy of different dosing intervals of colistin. We provide the subgroup analysis for the efficacy of different antibiotics plus colistin. In this study, we also conducted a publication bias analysis. However, there are some limitations: 1) lack of sufficient RCTs on both combination therapy and dosing intervals to include in our study, 2) the results were not stratified by infection type and type of organism. 3) because of the heterogenicity of the studies for dosing intervals, we could not conduct a meta-analysis

In conclusion, it seems that combination therapy, particularly colistin plus Meropenem, is associated with drug synergism and result in increased survival and efficacy. However, it is not statistically significant. The extended interval of colistin administration may result in higher peak concentration and bacterial eradication. In both cases, we face a dearth of literature, and thus a need for a randomized, controlled clinical trials to investigate dosing interval of colistin administration and the efficacy and safety of combination therapy.

List of acronyms

BSI – Bloodstream infection
CI - confidence interval
CMS - colistimethate sodium
ICU - intensive care unit
MDR - with multi-drug resistence
OR - odds ratio
RCT - randomized controlled trials
RR - risk ratio
VAP - ventilator-associated pneumonia
XDR - patients extensively drug-resistan

Contributions of Authors

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Conflict of Interest

The authors declare no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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