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 I² 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 ventilatorassociated 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) Gramnegative 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-

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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 fulltext 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

Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weight
Abdelsalam	5	30	13	30		0.26	[0.08; 0.87]	2.3%
Avdemir et al.	13	21	16	22	- <u></u>	0.61	[0.17; 2.21]	2.1%
Batirel	52	171	26	36		0.17	0.08; 0.37]	3.7%
Capone	12	37	4	11	<u> </u>	0.84	[0.21; 3.43]	1.8%
Daikos	0	8	4	15		0.15	[0.01: 3.18]	0.5%
Daikos	8	24	12	22		0.42	[0.13; 1.37]	2.3%
Durante-Mangoni	45	104	45	105	*	1.02	[0.59; 1.76]	5.0%
Falagas	7	16	1	4		2.33	[0.20; 27.57]	0.7%
Garnacho-Montero	14	29	14	28	<u></u>	0.93	[0.33; 2.64]	2.8%
Hernandez-Torres	5	19	2	4		0.36	[0.04: 3.26]	0.9%
Kalin	21	35	33	47		0.64	[0.25: 1.60]	3.2%
Katip	119	233	63	132		1.14	[0.75: 1.75]	5.8%
Katip (a)	49	131	63	193	*1	1.23	[0.77: 1.96]	5.5%
Katip (b)	59	124	72	124		0.66	[0.40; 1.08]	5.3%
Kontopidou	6	26	12	26		0.35	[0.11: 1.16]	2.3%
Ku	7	19	26	71	-	1.01	[0.35: 2.88]	2.7%
Lopez-Cortes	6	27	12	46		0.81	[0.26; 2.48]	2.5%
Makris	6	20	16	19		0.08	[0.02: 0.38]	1.6%
Mouloudi	9	18	18	35	_ <u>+</u>	0.94	[0.30; 2.94]	2.5%
Navarro	10	17	0	1		4.20	[0.15: 117.92]	0.4%
Nutman	37	73	86	198	-	1.34	[0.78: 2.29]	5.1%
Ozvatan	50	89	3	6		1.28	0.25: 6.701	1.4%
Papadimitriou	1	5	1	2		0.25	[0.01; 8.56]	0.4%
Parchem	19	41	21	49	-	1.15	[0.50; 2.65]	3.6%
Park H	1	4	1	5		1.33	[0.06: 31.12]	0.5%
Park J	19	52	10	32		1.27	[0.50: 3.23]	3.1%
Park,S	8	31	19	40		0.38	[0.14; 1.06]	2.8%
Paul	94	208	86	198		1.07	[0.73; 1.59]	6.0%
Petrosillo	35	105	17	61		1.29	[0.65; 2.58]	4.2%
Pintado	15	52	1	8		2.84	[0.32: 25.09]	0.9%
Porwal	13	29	8	12		0.41	[0.10; 1.66]	1.8%
Shi	20	83	16	77		1.21	[0.57: 2.55]	4.0%
Simsek	10	31	10	20		0.48	[0.15: 1.51]	2.4%
Sirijatuphat	22	47	27	47		0.65	[0.29; 1.47]	3.7%
Souli	8	12	1	2		2.00	[0.10: 41.00]	0.5%
Tumbarllo	14	51	11	22		0.38	[0.13; 1.07]	2.8%
Yilmaz	30	52	7	17		1.95	[0.64: 5.92]	2.5%
Zarkotou	0	14	4	7		0.03	[0.00; 0.62]	0.5%
Random effects mode		2088		1774	•	0 77	[0.62: 0.95]	100.0%

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 metaanalysis. 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 allcause 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 groups, which received the maximum two 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 extendedinterval 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 12hourly regimens do not provide the most effective

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Aaitp (b) Kaitp (b) Nutman Park,J Park,J Park,S Paul Shi Yilmaz Random effects me Heterogeneity: $l^2 = 65$ AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: $l^2 = 0\%$ AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: $l^2 = 0\%$ AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: $l^2 = 0\%$ AB = Tigecycline Daikos Kontopidou Random effects me Heterogeneity: $l^2 = 0\%$ AB = Tigecycline Daikos Kontopidou Random effects me Heterogeneity: $l^2 = 0\%$	$\begin{array}{c} & 0 \\ 9 \\ 59 \\ 59 \\ 59 \\ 7^2 \\ 14 \\ 8 \\ 94 \\ 20 \\ 16 \\ 00 \\ 16 \\$	131 124 73 391 31 208 83 33 869 p < 0.0 21 104 4 129 76 69 35 20 21 104 4 129 76 124 p < 0.0 124 p < 0.0 124 46	43 72 86 10 19 86 16 7 1 1 16 45 1 1 26 33 7 1 12 12	193 193 124 198 32 40 198 77 17 982 22 105 5 132 22 132 36 47 100 226 48		0.15 0.66 1.23 0.66 1.34 1.23 0.38 1.07 1.21 1.34 0.74 0.61 1.02 1.33 0.95 0.18 0.68 0.35 0.16 0.25	[0.07; [0.40; [0.78; [0.46; [0.14; [0.73; [0.57; [0.48; [0.44]; [0.48; [0.44]; [0.48; [0.58; [0.58; [0.58; [0.25; [0.86; [0.14; [0.09; [0.03; [0.09;	3.16] 1.96] 1.96] 2.29] 3.33] 1.06] 1.59] 2.55] 4.39] 1.13] 2.21] 1.76] 31.12] 1.66] 0.44] 1.66] 12.98] 3.41] 1.32] 0.82] 0.72]
Katip (a) Katip (b) Nutman Park, J Park, J Park, S Paul Shi Yilmaz Random effects me Heterogeneity: $I^2 = 65$ AB = Rifampin Aydemir et al. Durante-Mangoni Park, H Random effects me Heterogeneity: $I^2 = 0\%$ AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: $I^2 = 8\%$ AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: $I^2 = 0\%$ AB = Tigecycline Daikos Kontopidou Katenopidou Kontopidou Kontopidou Kontopidou Kontopidou Katenopidou Katenopidou Kontopidou Kontopidou Kontopidou Kontopidou Katenopi	$\begin{array}{c} 49\\ 59\\ 37\\ 14\\ 8\\ 94\\ 20\\ 16\\ 6, \tau^2 = 0.3392, \\ 13\\ 45\\ 1\\ 0del\\ 6, \tau^2 = 0, p = 0. \\ 22\\ 21\\ 14\\ 6, \tau^2 = 1.7377, \\ 1de\\ 5\\ 0del\\ 6, \tau^2 = 0, p = 0. \\ 5\\ \end{array}$	131 124 73 39 31 208 83 33 369 <i>p</i> < 0.0 21 104 4 129 76 69 35 20 224 <i>p</i> < 0.0 124 <i>p</i> < 0.0 17 17 34	63 72 86 10 19 86 16 45 1 1 26 33 7 1 1 26 33 7	193 124 198 32 40 198 77 17 982 22 105 5 132 22 105 5 132 366 47 17 100 222 266 48		0.66 1.34 1.23 0.38 1.07 1.21 1.34 0.74 0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.77; [0.40; [0.78; [0.46; [0.14; [0.57; [0.41; [0.59; [0.68; [0.68; [0.68; [0.68; [0.14; [0.25; [0.86; [0.14;] [0.09; [0.03; [0.09;	1.96] 1.08] 2.29] 3.33] 1.06] 1.59] 2.55] 4.39] 1.13] 2.21] 1.76] 31.12] 1.56] 0.44] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
Katip (D) Nutman Park,J Park,S Paul Shi Yilmaz Random effects me Heterogeneity: $l^2 = 65$ AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: $l^2 = 0\%$ AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: $l^2 = 84$ AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: $l^2 = 0\%$ AB = Tigecycline Daikos Kontopidou Random effects me Heterogeneity: $l^2 = 0\%$	59 37 14 8 94 20 0 16 0 0 16 16 16 16 16 16 16 16 16 16	124 73 39 31 208 83 33 869 p < 0.0 21 104 4 129 76 69 355 20 124 p < 0.0 17 17 34 46	72 86 10 19 86 16 45 1 1 26 33 7 1 12 12	124 198 32 40 198 77 17 982 22 105 5 132 36 47 100 22 26 48		0.66 1.34 1.23 0.38 1.07 1.21 1.34 0.74 0.61 1.02 1.03 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.40; [0.78; [0.46; [0.14; [0.57; [0.57; [0.41; [0.44; [0.44; [0.44]; [0.48; [0.58; [0.58; [0.58; [0.66; [0.58; [0.25; [0.86; [0.14; [0.09; [0.03; [0.09;	1.08] 2.29] 3.33] 1.06] 1.59] 2.55] 4.39] 1.13] 2.21] 1.76] 31.12] 1.76] 31.12] 1.66] 12.98] 3.41] 1.32] 0.82] 0.72]
Nutman Park,J Park,J Park,J Park,S Park,S Park,S Park,S Park,S Random effects me Heterogeneity: I ² = 65 AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: I ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: I ² = 84 AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: I ² = 0% AB = Tigecycline Daikos Kontopidou Kata = Tigecycline Daikos Kontopidou Kapadimitriou Papadimitriou Park,J Random effects me	37 14 8 94 94 20 16 94 20 16 94 20 16 94 20 16 94 20 16 94 20 16 94 20 16 94 20 16 94 20 16 94 20 16 94 20 16 94 20 20 20 20 20 21 21 21 21 21 21 21 21 21 21	73 39 31 208 83 33 869 p < 0.0 21 104 4 129 76 69 35 200 124 p < 0.0 17 17 34 46	86 10 19 86 16 45 1 1 26 33 7 7 1 12 12	198 32 40 198 77 17 982 22 105 5 132 36 47 17 100 22 26 48		1.34 1.23 0.38 1.07 1.21 1.34 0.74 0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.78; [0.46; [0.14; [0.73; [0.57; [0.41; [0.41; [0.48; [0.41; [0.59; [0.68; [0.68; [0.68; [0.68; [0.06; [0.06; [0.14; [0.09; [0.09; [0.09;	2.29] 3.33] 1.06] 1.59] 2.55] 4.39] 1.13] 2.21] 1.76] 31.12] 1.56] 0.44] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
Park,J Park,S Paul Shi Yilmaz Random effects me Heterogeneity: /² = 65 AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: /² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: /² = 84 AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: /² = 0% AB = Tigecycline Daikos Kontopidou Random effects me Heterogeneity: /² = 0% AB = Tigecycline Daikos Kontopidou Random effects me Heterogeneity: /² = 0% AB = Tigecycline Daikos Kontopidou Random effects me	14 8 94 16 odel 16 odel 18 odel 19 6, $\tau^2 = 0.3392$, 13 45 10 14 16 16 16 16 16 16 16 16 16 16	39 31 208 83 33 869 p < 0.0 21 104 4 129 76 69 355 20 124 p < 0.0 124 p < 0.0 124 46	10 19 86 16 45 1 26 33 7 1 1 212	32 40 198 77 17 982 22 105 5 132 36 47 17 100 226 48		1.23 0.38 1.07 1.21 1.34 0.74 0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.46; [0.14; [0.57; [0.41; [0.48; [0.48; [0.58; [0.58; [0.66; [0.58; [0.66; [0.58; [0.25; [0.86; [0.14;] [0.09; [0.03; [0.09;	3.33] 1.06] 1.59] 2.55] 4.39] 1.13] 1.76] 31.12] 1.76] 31.12] 1.66] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
Park, S Paul Shi Shi Random effects me Heterogeneity: I ² = 65 AB = Rifampin Aydemir et al. Durante-Mangoni Park, H Random effects me Heterogeneity: I ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: I ² = 84% AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: I ² = 0% AB = Tigecycline Daikos Kontopidou Ku AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Park, J Random effects me	$\begin{array}{c} 8\\ 94\\ 94\\ 20\\ 16\\ 16\\ 16\\ 16\\ 16\\ 16\\ 10\\ 13\\ 45\\ 10\\ 10\\ 13\\ 45\\ 10\\ 10\\ 12\\ 13\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10$	31 208 83 33 869 p < 0.0 21 104 4 129 76 69 35 20 20 80 76 124 .p < 0.0 17 17 34	19 86 16 7 1 16 45 1 1 26 33 7 1 12 12	40 198 77 17 982 22 105 5 132 36 47 17 100 22 26 48		0.38 1.07 1.21 1.34 0.74 0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.14; [0.73; [0.57; [0.41; [0.41; [0.48; [0.59; [0.59; [0.68; [0.68; [0.68; [0.71; [0.25; [0.86; [0.14;] [0.09; [0.03; [0.09;	1.06] 1.59] 2.55] 4.39] 1.13] 2.21] 1.76] 31.12] 1.56] 0.44] 1.80] 12.98] 3.41] 1.32] 0.82] 0.72]
Paul Shi Yilmaz Random effects me Heterogeneity: $I^2 = 65$ AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: $I^2 = 0\%$ AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: $I^2 = 8\%$ AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: $I^2 = 0\%$ AB = Tigecycline Daikos Kontopidou Random effects me Heterogeneity: $I^2 = 0\%$ AB = Tigecycline Daikos Kontopidou Random effects me Kontopidou Random effects me	94 20 16 odel 16, $\tau^2 = 0.3392$, 13 45 10 16 10 16 17 17 16 16 16 17 17 16 16 16 16 16 16 16 16 16 16	208 83 33 869 p < 0.0 21 104 4 129 76 69 35 20 124 p < 0.0 124 p < 0.0 124 46	86 16 7 1 16 45 1 26 33 7 1 12 12	198 77 17 982 22 105 5 132 36 47 17 100 22 26 48		1.07 1.21 1.34 0.74 0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.73; [0.57; [0.41; [0.48; [0.59; [0.58; [0.66; [0.58; [0.68; [0.77; [0.25; [0.86; [0.14;] [0.09; [0.03; [0.09;	1.59 2.55 4.39 1.13 1.76 31.12 1.76 31.12 1.66 0.44 1.60 12.98 3.41 1.32 0.82 0.72
Shi Yilmaz Random effects me Heterogeneity: I ² = 65 AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: I ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: I ² = 84% AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: I ² = 0% AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Park,J Random effects me	20 16 16 16 16 16 16 16 16 17 17 18 19 19 19 19 19 19 19 19 19 19	83 869 p < 0.0 21 104 4 129 76 69 35 20 124 p < 0.0 17 17 34 46	16 7 16 45 1 26 33 7 1 12 12	77 17 982 22 105 5 132 36 47 17 100 22 26 48		1.21 1.34 0.74 0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.57; [0.41; [0.48; [0.59; [0.59; [0.66; [0.68; [0.68; [0.07; [0.25; [0.86; [0.14;] [0.09; [0.03; [0.09;	2.55] 4.39] 1.13] 2.21] 1.76] 31.12] 1.56] 0.44] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
Yilmaz Random effects me Heterogenety: / ² = 65 AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogenety: / ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogenety: / ² = 84 AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogenety: / ² = 0% AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Park,J Random effects me	16 odel 16, $\tau^2 = 0.3392$, 13 45 10 14 14 14 14 14 14 14 14 14 14	33 869 p < 0.0 21 104 4 129 76 69 35 20 124 p < 0.0 124 4 17 34 46	7 16 45 1 26 33 7 1 12 12	17 982 22 105 5 132 36 47 17 100 22 26 48		0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.41; [0.48; [0.59; [0.66; [0.58; [0.68; [0.77; [0.25; [0.86; [0.14; [0.14; [0.09; [0.03; [0.09;	4.39 1.13 2.21 1.76 31.12 1.56 0.44 1.66 0.44 1.298 3.41 1.32 0.82 0.72
Andom effects me Heterogeneity: <i>I</i> ² = 65 AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: <i>I</i> ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: <i>I</i> ² = 8% AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: <i>I</i> ² = 0% AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Park,J Random effects me	odel $\%, \tau^2 = 0.3392,$ 13 45 10 10 10 12 13 45 10 14 14 14 14 14 16 16 16 17 17 16 16 16 17 16 16 17 16 16 17 16 16 16 16 16 16 16 16 16 16	21 104 4 129 76 69 35 20 124 .p < 0.0 17 17 34 46	1 16 45 1 26 33 7 1 12 12	982 22 105 5 132 36 47 17 100 22 26 48		0.74 0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.48; [0.48; [0.59; [0.59; [0.68; [0.68; [0.25; [0.86; [0.14; [0.09; [0.03; [0.09;	1.13] 2.21] 1.76] 31.12] 1.66] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
Random effects me Avdemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: I ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: I ² = 84 AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: I ² = 0% AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Paradom effects me	http://www.communications.communica	21 104 4 129 76 69 35 20 124 , p < 0.0 124 , p < 0.0 17 17 34 46	16 45 1 26 33 7 1 12 12	22 105 5 132 36 47 17 100 22 26 48	+++++++++++++++++++++++++++++++++++++++	0.61 1.02 1.33 0.95 0.18 0.68 0.68 0.35 0.16 0.25	[0.48, [0.59; [0.68; [0.68; [0.25; [0.86; [0.14; [0.14; [0.09; [0.03; [0.09;	2.21] 1.76] 31.12] 1.56] 0.44] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
AB = Rifampin Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogeneity: / ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: / ² = 84 AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: / ² = 0% AB = Tigecycline Daikos Kontopidou Katopidou Kuntopidou Kuntopidou Kuntopidou Kuntopidou Kuntopidou Katopidou Kuntopidou Ka	13 45 1 b, $\tau^2 = 0, p = 0$. 22 21 14 odel %, $\tau^2 = 1.7377$, ide 5 odel b, $\tau^2 = 0, p = 0$. 5	$21 \\ 104 \\ 4 \\ 129 \\ 76 \\ 69 \\ 35 \\ 20 \\ 124 \\ p < 0.0 \\ 17 \\ 17 \\ 34 \\ 46 \\ 46 \\ $	16 45 1 26 33 7 1 12 12	22 105 5 132 36 47 17 100 22 26 48		0.61 1.02 1.33 0.95 0.18 0.64 3.33 0.68 0.35 0.16 0.25	[0.17; [0.59; [0.06; [0.68; [0.25; [0.86; [0.14; [0.09; [0.03; [0.09;	2.21] 1.76] 31.12] 1.56] 0.44] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
Aydemir et al. Durante-Mangoni Park,H Random effects me Heterogenety: / ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogenety: / ² = 84 AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogenety: / ² = 0% AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Park,J Random effects me	13 45 1 b_{1} $\tau^{2} = 0, p = 0.$ 22 21 14 odel 96, $\tau^{2} = 1.7377.$ ide 5 odel b_{1} $\tau^{2} = 0, p = 0.$	21 104 4 129 76 69 35 20 124 .p < 0.0 17 17 34 46	16 45 1 26 33 7 1 12 12	22 105 5 132 36 47 17 100 22 26 48	++ ++ ++ ++ ++ ++	0.61 1.02 1.33 0.95 0.18 0.68 0.68 0.35 0.16 0.25	[0.17; [0.06; [0.06; [0.25; [0.25; [0.86; [0.14; [0.09; [0.03; [0.09;	2.21] 1.76] 31.12] 1.56] 0.44] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
Durante-Mangoni Park,H Random effects me Heterogeneity: / ² = 0% AB = Sulbactam Batirel Kalin Yilmaz Random effects me Heterogeneity: / ² = 84 AB = Aminoglycosi Daikos Kontopidou Random effects me Heterogeneity: / ² = 0% AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Park,J Random effects me	45 odel 1 $b, \tau^2 = 0, p = 0.$ 22 21 14 odel 14 96, $\tau^2 = 1.7377.$ ide 5 odel 6, $\tau^2 = 0, p = 0.$	104 4 129 76 69 35 20 124 , p < 0.0 17 17 34 46	45 1 26 33 7 1 12 12	105 5 132 36 47 17 100 22 26 48	*	1.02 1.33 0.96 0.18 0.64 3.33 0.68 0.35 0.35 0.16 0.25	[0.59; [0.06; [0.58; [0.25; [0.86; [0.14; [0.09; [0.03; [0.09;	1.76] 31.12] 1.56] 0.44] 1.60] 12.98] 3.41] 1.32] 0.82] 0.72]
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AB = Tigecycline Daikos Kontopidou Ku Papadimitriou Park,J Random effects mo	5							
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Kontopidou Ku Papadimitriou Park,J Random effects mo		21	12	22		0.26	[0.07;	0.96]
Ku Papadimitriou Park,J Random effects mo	4	9	12	26		0.93	[0.20;	4.291
Papadimitriou Park,J Random effects mo	7	19	26	71		1.01	10.35:	2.881
Park,J Random effects mo	1	2	1	2		- 1.00	[0.02:	50.401
Random effects me	5	13	10	32		1.38	10.36:	5 271
Heterogeneity: $I^2 = 0\%$	odel $x^2 = 0.0686$ (64		153	4	0.78	[0.39;	1.53]
AB = Vancomucin		0.10						
Carpacho Montoro	14	20	14	20		0.02	10 22	2641
Katie	110	222	63	122	1_	1.14	10.75	1 751
Kaup	119	233	03	132	T	1.14	10.75,	1.75]
Heterogeneity: $I^2 = 0\%$	$b_{1}, \tau^{2} = 0, p = 0.$	72		160	Ť	1.11	[0.75;	1.65]
	Difamplein							
Hernandez-Torree	5	19	2	4		0.36	10.04	3 261
Pandom effects	Isho	10	-			0.26	10.04	3 261
Heterogeneity: not app	blicable	15				0.50	[0.044,	5.20]
AB = Ampicilin-Sul	bactam							
Makris	6	20	16	19		0.08	[0.02]	0.381
Random effects m	Isho	20		19		0.08	10.02	0 381
Heterogeneity: not app	olic able	2.0		10		0.00	Lo.o.z.,	0.001
AB = Gentamicin								
Mouloudi	9	18	18	35		0.94	[0.30]	2.941
Papadimitriou	0	3	1	2 -		0.14	10.00	5 951
Souli	9	12		2		2.00	10 10	41 001
Dandom offente	o	22		20		2.00	10.10,	2 401
Heterogeneity: $l^2 = 0\%$	$b, \tau^2 = 0, p = 0.$	55		29	T	0.89	[0.32;	2.48]
AB = Fosfomycin	-	17				0.05	10 00	4
Sinjatuphat et al.	22	47	21	47		0.65	[0.29;	1.47]
Random effects mo	odel	47		47	-	0.65	[0.29;	1.47]
Heterogeneity: not app	olicable							
Heterogeneity: $I^2 = 55'$	$\%, \tau^2 = 0.3107$	p < 0.0	1					

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



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 metaanalysis 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 multidrugresistant 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 metaanalysis

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

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Conflict of Interest

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