The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 5451-5458

Colistin Versus Colistin & Meropenem in Extensively Resistant Enterobacterales Organisms Therapy in Critically Ill Patients

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ABSTRACT

Background: Extensively drug resistant (XDR) organisms like Acinetobacter baumannii, pseudomonas aeruginosa XDR, Klebsiella pneumoniae XDR and Carbapenem-resistant Enterobacterales (CRE) leading to pneumonia and blood stream infections (BSI) are associated with high mortality rates and therapeutic modalities became restricted.

Objective: Our clinical trial assessed whether combination therapy with Colistin and meropenem was superior to colistin alone for treatment of the extensively drug resistant Enterobacterals.

Patients and methods: Our study was a randomized, prospective trial, we randomly selected the participants to receive Colistin loading dose of 5 mg/kg once followed by a maintenance dose of 1.67 mg/kg every 8 hours in Combination with either meropenem at a dose of 2 gm every 8 hours or Colistin alone, for treatment of pneumonia and/or Blood stream infection (BSI) caused by extensively resistant (XDR) Acientobacter baumannii, pseudomonas aeruginosa XDR, Klebsiella pneumoniae XDR and Carbapenem resistant Enterobacterals.

Results: Two hundred participants were randomly assigned to treatment by either Colistin as monotherapy or by combination of Colistin and meropenem. Acinetobacter baumannii and Klebsiella pneumoniae were the predominant organisms in our study (67%) and (16%) respectively followed by carbapenem-resistant Enterobacterals (15%) and pneumonia the most common infection (80%). All patients were in the intensive care unit at the time of enrollment (100%). There was a statistical difference in mortality between both groups (79% in colistin group and in combination therapy group was 48%; $p < 0.001$), clinical improvement (vasopressor requirement, mechanical ventilation settings, inflammatory markers, leucocytic count and radiology) were all in favor of the Combination therapy of Colistin and meropenem.

Conclusion: Colistin and meropenem Combination therapy was more beneficial than monotherapy only for the treatment of pneumonia and/or blood stream infection caused by the XDR Entrobacterals including mortality.

Keywords: Colistin, meropenem, XDR organisms.

INTRODUCTION

Extensively drug-resistant XDR Acientobacter, XDR Klebsiella pneumoniae, XDR pseudomonas acruginosa and carbapenem resistant Enterobacterales (CRE) causing pneumonia and blood stream infections are associated with a ruined outcomes[(1-4)].

The World Health organization together with the U.S. Centers for Disease Control and prevention recognizes these pathogens as serious or urgent threats to human health[(5)], and they highlighted that they are of the highest priority for research and development of new therapeutic agents given the rarity of treatment options[(6)]. Despite the revival of novel agents in the past decade for the treatment of Carbapenem resistant gram negative pathogens, unmet needs remain. Novel agents are not universally available and not active against all Carbapenem-resistant pathogens and following their adoption in clinical practice, resistance to these agents has proliferated[(7)].

Colistin therefore remains an essential and frequently used agent for the management of infections due to XDR gram-negative bacilli in the united states and worldwide[(8)].

Concerns exist regarding Colistin's safety and efficacy as monotherapy[(9)]. In Vitro potency synergy of colistin when combined with carbapenems, many experts recommend that colistin be combined with a carbapenem for the treatment of infections caused by Carbapenem, resistant gram-negative bacilli, despite the presence of carbapenem resistance and a lack of solid clinical evidence supporting this strategy. Importantly, there are significant risks associated with wide spread carbapenem use, including further resistance development and increase in adverse events including clostridium difficile-associated disease[(10, 11)].

Our study is a randomized prospective trial assessing outcomes in carbapenem–resistant gram-negative bacilli was designed to evaluate whether combination therapy with colistin and a carbapenem is superior to colistin monotherapy.

PATIENTS AND METHODS

Our study was a randomized prospective trial conducted in Helwan University Hospitals in Critical Care Medicine Department Faculty of Medicine Helwan University in the period from August 2020 to October 2022.

Eligible patients were more than 18 years old and had pneumonia and/or bloodstream infection (BSI) caused by XDR A. baumannii, XDR pseudomonas

Received: 08/11/2022
Accepted: 08/01/2023

aeruginosa, XDR Klebsielia pneumoniae or CRE with in vitro susceptibility to colistin (Colistin minimum inhibitory concentration [MIC] ≤ 2mg/L, patients were ineligible if they received 72 hours or more of polymixin treatment within 96 hours of enrollment or if they had life expectancy of 24 hours or less [12].

Patients were enrolled in the trial based on carbapenem and Colistin susceptibility test results performed in the microbiology laboratory of Helwan University Hospitals.

Confirmatory susceptibility testing by broth microdilution (BMD) for all available isolates was performed in the microbiology laboratory of Helwan University Hospitals. Isolates were Colistin susceptible by other methods other than BMD and the patient received on trial treatment but index pathogen was subsequently found to be colistin resistant by BMD, patients were excluded from the modified intention to treat (mITT) analysis.

Colistin was given to all participants with a loading dose of 5 mg/kg followed by 1.67 mg/kg every 8 hours, also participants were randomly assigned to receive intravenous carbapenem of a dose 2 gm every 8 hours extended infusion over 3 hours namely meropenem.

All doses were adjusted renally, the duration of therapy was 7 to 14 days. Balanced block randomization was of eight separate sequences defined according to infection type, organism confirmatory status, and for patients with pneumonia only, severity of illness measured by the acute physiology and chronic Health Evaluation II [APACHE II] score[13], with patients stratified according to scores < 25 vs ≥ 25). APACHE II has a range of scores from 0 to 71, and an APACHE II score of 25 is associated with a predicted in hospital mortality of 55%.

No more stratification was made for the pneumonia group but patients with blood stream infection were more stratified according to primary (the BSI is not secondary to other sources) versus secondary (the BSI is secondary to infection at a distal site) bacteremia[14].

The intention to treat (ITT) population consisted of all randomly assigned patients, the mITT population included all randomly assigned patients with a trial pathogen who received at least one dose of trial medication and whose trial pathogens exhibited colistin susceptibility according to BMD.

All treated population included all patients in the mITT population except the persons showing colistin resistance according to the BMD testing. Patients with BSI, blood cultures were taken daily until they were negative for two consecutive days. Also pneumonia patients, sputum cultures were withdrawn daily until they were negative for two consecutive days.

The primary outcome was all cause 28 day mortality in the mITT population.

Secondary efficiency outcomes including clinical failure and microbiological cure were evaluated in patients who survived more than 48 hours after enrollments completing trial therapy for any reason other than meeting clinical failure criteria were deemed in determinant for clinical failure and were subsequently excluded from this end point.

Clinical failure was a combined end point defined as meeting any of the following: death either while on trial therapy or within 7 days following completion; receipt of rescue therapy for the trial pathogen within 7 days of completion of trial treatment; removal from the trial due to an adverse event considered related to trial treatment, bactermia more than 5 days after initiation of trial treatment for patients with blood stream infection or failure to improve or worsening of oxygenation by the end of trial treatment in patients with pneumonia.

For patients with pneumonia who were mechanically ventilated at baseline improvement of oxygenation was defined as any of the following occurring by the end of trial therapy, removal from mechanical ventilation, an increase in the ratio of arterial oxygen partial pressure to the fraction of inspired oxygen (Pao_2/Fio_2) by 100 mmHg, or an increase in Pao_2/Fio_2 to a value of 300 mmHg or higher.

For patients who remained on mechanical ventilation at the end of trial treatment without improvement in Pao_2/Fio_2 ratio were considered treatment failure. Microbiological cure was only assessed for patients in whom repeat specimens were obtained and was defined as eradication of pathogen from the infection site (i.e. negative culture) by the end of treatment.

For trial patients with pneumonia who completed a full course of trial therapy but did not have a documented negative respiratory culture, microbiological outcomes were determined by the date of last recorded positive respiratory sample according to the following criteria.

If the patient's last respiratory culture was positive and was collected 7 or more days after trial enrollment, they were considered a microbiological failure.

If the patient's last respiratory culture was positive and obtained 7 days or less after enrollment, the patient was classified as microbiological failure as no interference could be made with respect to eradication at the end of therapy.

Also if a patient was removed from the trial early due to death or treatment failure before documented eradication of the pathogen from the respiratory sample, they were considered as a microbiological safety outcomes evaluated included decreases in renal function. Acute kidney injury (AKI) was defined according to the RIFLE (Risk, Injury, failure, loss of kidney function and End-stage kidney disease) criteria[15].

All patients who received a trial drug for 48 hours or more with a baseline creatinine clearance of 30 ml/min or higher were eligible for AKI assessment, regardless of whether they remained in the mITT population.

Ethical consent:

The study was authorized by Helwan University's Ethical Institutional Review Board. All study participants provided written informed permission after being informed of our research's goals. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical Analysis

The collected data was revised, coded, tabulated and introduced to a PC using statistical package for social science (SPSS 25). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Mean, standard deviation (± SD) for numerical data. Frequency and percentage of non-numerical data. Student T test was used to assess the statistical significance of the difference between two study group means. Chi-square test was used to examine the relationship between two qualitative variables. P value < 0.05 was considered significant.

The primary mortality analysis used a chi-square test and associated Kaplan-Meier survival curve estimation and log-rank testing. Cox regression was used for secondary survival analysis. The t-tests or Will coxon rank-sum tests were used to assess other continuous or ordinal variables as appropriate. For secondary outcomes, pre-specified multiple comparison adjustment was included in the statistical analysis plan and thus a significance tests are presented for those outcomes. Instead only the estimated percentage-point differences [Colistin] – [Colistin plus meropenem] and associated t-test. Patients who were indeterminent in terms of the improvement in oxygenation criteria were assessed based on the other components of the composite outcome. Those who met another component of clinical failure were considered clinical failures where as those who did not meet any other failure criteria were considered not to be failures.

RESULTS

A total of 200 patients were enrolled randomly assigned to our trial, all met the inclusion criteria and comprised the mITT population.

The mITT population included 200 patients, one hundred patients received colistin alone and 100 received colistin in combination with menopenem.

Baseline characteristics of patients in the two treatment arms, the mean age was 47.54 ± 8.36 in colistin group and 47.74 ± 8.42 in the combination group colistin and meropenem, 62 males and 38 females in the colistin group while 61 males and 39 females in the combination group all were non-significant statistically. The most frequent co-morbidities, were hypertension of 62% in colistin group and 64% in the combination group, Diabetes 78% in colistin group and 79% in the combination group.

All patients enrolled were in the intensive care unit & critically ill. pneumonia was the most common type of index infection 80% 160 out of the two hundred, 40 patients out of the 160 patient they had concomitant bloodstream infection (BSI), the remaining 40 patients had only BSI.

The most common pathogen was Acientobacter baumannii 67% 134 patient, followed, by Klebsiella pneumeniae 16%, CRE 15%, and pseudomonas acruginosa 2%, twenty three patients 11.5% had multiple trial pathogens as the cause of their index infection and 31% were co-infected with a non-trial pathogen.

The median time from onset of index infection to administration of the appropriate therapy i.e. therapy with in vitro activity against the trial pathogen was 4 days (interquartile range 3-5 days).

Before enrollment, 83% of the patients in the study this means that 166 patient received a median of 2 days of treatment with a drug active against the trial pathogen. When a patient received a non-trial drug active against the trial pathogen before enrollment, the drug in almost cases was colistin. 78% patients who received an active, non-trial drug before enrollment received colistin in combination with meropenem for a median duration of 2 days before enrollment.

There was significant statistical difference in 28-day mortality between the colistin monotherapy and colistin plus meropenem combination therapy in favor of the combination therapy 48% vs 79% in the colistin group with p-value <0.001 and there was difference in time to mortality.

Also there was difference in mortality between the two treatment arms in all infection type or pathogen subgroup. When assessing 28-day mortality according to time to appropriate therapy or when excluding patients who received pre-enrollment colistin plus meropenem combination therapy or who were co-infected with non-trial pathogens; there remained still difference between treatment arms.

All the two hundred patients were eligible for analysis of the clinical failure end point. There was a statistical difference in clinical cure between the monotherapy and the combination therapy as regard the vasopressor weaning and stoppage 78% in the combination therapy versus, 49% in the monotherapy group, mechanical ventilation improvement and weaning 80% in the combination therapy, group versus 46% in the monotherapy group, CRP 80%, versus 48%, total leucocytic count 78% versus 50%, arterial blood gas (ABG) criteria. pH 75% versus 47%, PCO_2 78% versus 47%, PO_2 76% versus 49% HCO_3 77% versus 5.3%, lactate 78% versus 51 and also renal function represented by creatinine and urea 76% versus 52%, when compared the combination therapy to the monotherapy respectively all in favor of the combination therapy with a highly significant statistical difference.

Microbiological cure was 76% in the combination therapy group versus 52% in the monotherapy group.

Table (1): Showed the baseline characteristics in both groups

Demographic	Colistin N = 100	Colistin of Meropenem (n =100)
Age	47.54 ± 8.36	47.74 ± 8.42
Sex		
Male	62%	61%
Female	38%	39%
Comorbidities		
Hypertension	62%	64%
Diabetes mellitus	78%	79%
Key patient characters at time of infection onset		
Serum creatinine mg/dl	1.09 ± 1.2	1.03 ± 0.9
Intensive care residence – no (%)	100/100	100/100
Mechanical ventilation no (%)	80/100	79/100
APACHEII score- medium	16 (13-19)	16 (13-19)
Vasopressor use – no (%)	73/100	71/100
Infection type pneumonia	80/100	80/100
Pneumonia with secondary bacteremia	20/80	20/80
Blood stream infection	20/100	20/100
Infecting organism		
Acientobacter baumannii	67/100	67/100
Klebsiella pneumoniae	16/100	16/100
Enterobacterals pneumonia	15/100	15/100
Pseudomonas aeruginosa	2/100	2/100

Table (2): Showed Twenty-Eight day mortality in both groups

Cause of Mortality	Colistin	Colistin & Meropenem.	p-value	Sig.
Overall Mortality	79/100 (79%)	48/100 (48%)	<0.001	S
Pneumonia	60/80 (75%)	36/80 (45%)	< 0.001	S
BSI	16/20 (80%)	8/20 (40%)	<0.001	S
ACB	45/67 (67%)	21/67 (31%)	<0.001	S
Klebsiella	12/16 (75%)	7/16 (44%)	<0.001	S
CRE	12/15 (80%)	4/15 (27%)	<0.001	S
Pseudomonas Aeruginos	2/2 (100%)	1/2 (50%)	<0.001	S

All the 28-day mortality was in favor of the combination group (Colistin & Meropenem) when compared to the monotherapy group (colistin only) with a highly significant statistical difference p-value <0.001.

Table (3): SHOWED the secondary outcome compared between both groups.

	Colistin	Colistin & Meropenem	t-test	p-value	Sig.
Clinical Cure pneumonia	20/80 (25%)	44/80 (53%)	$X^2 = 22.82$	<0.001	S
Blood stream infection	4/20/(20%)	12/20 (60%)	$X^2 = 12.5$	<0.001	S
ACB	22/7 (33%)	46/67 (69%)	$X^2 = 18.14$	<0.001	S
Klebsiella	4/16 (25%)	9/16 (56%)	$X^2 = 12.5$	<0.001	S
CRE	3/15 (20%)	11/15 (73%)	$X^2 = 11.35$	<0.001	S
Pseudomenas aeruginosa	0/2 (0%	1/2(50%)	$X^2 = 13.75$	<0.001	S
Vasopressor weaning & stoppage	49/100 (49%)	78/100 (78%	$X^2 = 18.14$	<0.001	S
MV weaning	46/100 (46%)	80/100(78%)	$X^2 = 24.8$	<0.001	S
CRP	48/100 (48%)	80/100(80%)	$X^2 = 22.22$	<0.001	S
Improvement in TLC & nerutrophilia	47/100 (47%)	78/100(78%)	$X^2 = 20.5$	<0.001	S
Procalcitonin	55/100 (55%)	79/100 (79%)	$X^2 = 13.03$	<0.001	S
Radiology improvement	50/100 (50%)	82/100 (82%)	$X^2 = 22.82$	<0.001	S
ABG parameters pH	47/100 (47%)	75/100 (75%)	$X^2 = 16.48$	<0.001	S
PCO_2	47/100 (47%)	78/100 (78%	$X^2 = 20.5$	<0.001	S
PO_2	49/100 (49%)	76/100 (76%)	$X^2 = 15.55$	<0.001	S
HCO_3	53/100(53%)	77/100(77%)	$X^2 = 12.66$	<0.001	S
Lactate	51/100(51%)	78/100(78%)	$X^2 = 15.92$	<0.001	S
Renal function not affected	52/100(52%)	76/100(76%)	$X^2 = 12.5$	<0.001	S
Microbiological Cure overall	52/100(52%)	76/100(76%)	$X^2 = 12.5$	<0.001	S
Pneumonia	20/80(25%)	44/80(53%)	$X^2 = 22.82$	<0.001	S
BSI	4/20 (20%)	12/20 (60%)	$X^2 = 12.5$	<0.001	S
A.baumanii	22/67(33%)	46/67(69%)	$X^2 = 18.14$	<0.001	S
Klebsiella pneumoniae	4/16(25%)	9/16(56%)	$X^2 = 12.5$	<0.001	S
CRE	3/15(20%)	11/15(73%)	$X^2 = 11.37$	<0.001	S
Pseudomonas aeruginosa	0/2(0%)	1/2 (50%)	$X^2 = 13.75$	<0.001	S

All clinical cure parameters together with the microbiological cure all in favor of the combination therapy group Colistin & menopenem versus colistin group; with a statistically significant difference p-value <0.001.

Table (4): Cox regression analysis for secondary survival analysis

	HR (95% Cl)	Sig.
COLISTIN+MEROPNEM	0.27 (0.1-0.69)	0.006
Vasoprossor requirement	0.88 (0.56 – 1.38)	0.574
MV setting	0.78 (0.51 -1.18)	0.235
CRP	0.95 (0.6 – 1.49)	0.814
TLC with neutrophillia	1.31 (0.82-2.11)	0.262
Procalcitonin	1.27 (0.81-1.99)	0.568
Radiology	1.15 (0.72-1.82)	0.383
PH	1.23 (0.77-1.98)	0.383
PO2	0.92 (0.56 – 1.51)	0.729
HCO3	1.42 (0.91-2.22)	0.127
Lactate	0.92 (0.59 – 1.43)	0.696
Deterioration in Renal function	2.03 (1.23-3.34)	0.005
Microbiological Cure	0.32 (0.15 – 0.73)	0.007

Table (4) showed a better outcome in the combination group (Colistin and menopenem) versus the monotherapy group as regard the 28-day mortality with HR (95% CI) 0.27 (0.1-0.69) and p-value 0.006. Also the microbiological cure showed the association with decreasing the 28 day mortality with HR (95% CI) 0.32 (0.15 – 0.73) and p-value 0.007. While the deterioration in renal function was a risk to 28-day mortality HR (95% CI) 2.03 (1.23 – 3.34) and p-value 0.005, at the same time other secondary outcomes and parameters were all statistically in significant in relation to the 28 day mortality.

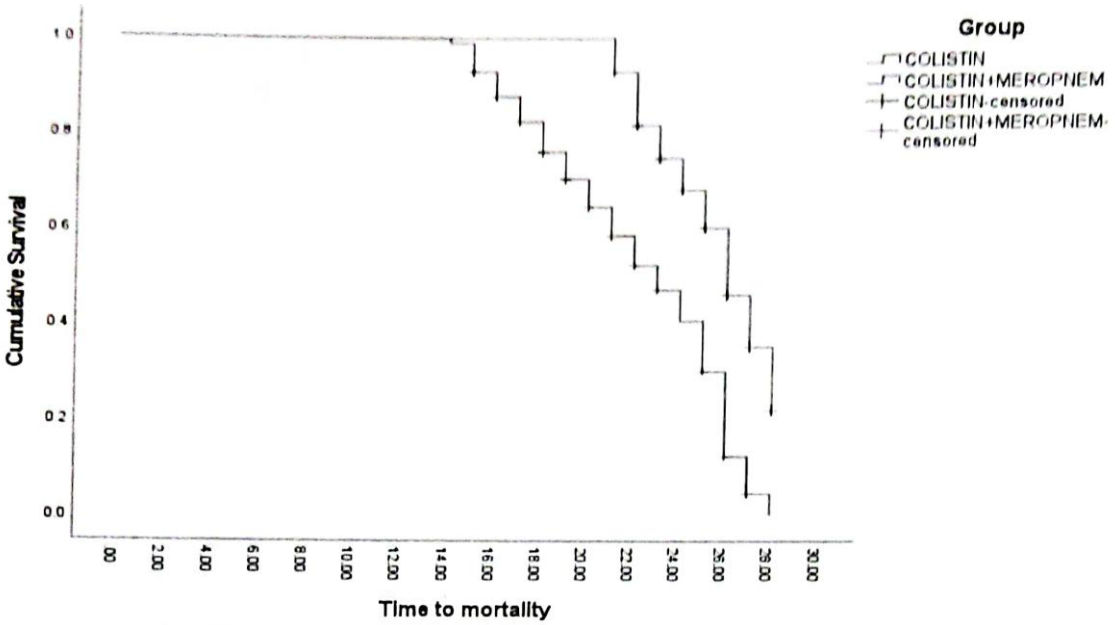

Figure (1): Kaplan Meier curve of survival for both group's combination therapy (colistin and meropenem) and monotherapy (colistin only).

Survival Table				
Group	**Time**	**Cumulative Proportion Surviving at the Time**		**N of Cumulative Events**
		Estimate	**SE**	
COLISTIN	14	99.0%	1.0%	1
	15	93.0%	2.6%	7
	16	87.9%	3.3%	12
	17	82.7%	3.8%	17
	18	76.3%	4.3%	23
	19	70.8%	4.7%	28
	20	64.9%	5.0%	33
	21	58.9%	5.2%	38
	22	51.6%	5.3%	43
	23	47.5%	5.4%	47
	24	40.9%	5.4%	52
	25	30.3%	5.1%	60
	26	12.4%	3.8%	73
	27	4.7%	2.6%	78
	28	0.0%	0.0%	79
	Time	**Cumulative Proportion Surviving at the Time**		**N of Cumulative Events**
		Estimate	**Estimate**	
COLISTIN + MEROPENAM	21	93.0%	2.6%	7
	22	81.9%	3.9%	18
	23	75.1%	4.4%	24
	24	68.5%	4.9%	29
	25	60.5%	5.5%	34
	26	46.4%	6.3%	41
	27	35.5%	6.8%	45
	28	22.2%	7.4%	48

	Mean ± SE	**95% CI**	**Log rank test**	
COLISTIN	22.22±0.42	21.39- – 23.04	p-value	**Sig.**
COLISTIN+MEROPNEM	25.61±0.27	25.09 – 26.13	<0.001	**S**
Overall	23.91 ± 0.27	23.38 – 24.44		

Kaplan Meir curve of 28-day mortality showed a better survival in the combination group. (colistin and meropenem) versus the monotherapy group, with a p-value <0.001.

DISCUSSION

In our prospective randomized trial, there was a statistical difference between the monotherapy colistin alone and the combination therapy group colistin plus meropenem in favor of the combination therapy as regard the primary outcome of 28-day mortality or the secondary out comes of clinical cure including the laboratory findings and markers and radiologically together with the complications like AKI and micro-biologically cure in patients with pneumonia or BSI caused by XDR gram negative pathogens or CRE this different from the findings from the recent open label trial AIDA (the European Union's Multicenter open label Randomised controlled Trial to compare colistin alone versus colistin plus Meropenem) that compared the same treatment regimen [17].

As our trial, AIDA trial consisted predominantly of A.baumannii infections (77%) with 88% of patients having either pneumonia or BSI other randomized controlled trials comparing colistin monotherapy versus combination therapy with colistin and either rifampin[18-19], or fosfomycin[20] for invasive A. baumannii infections have also failed to show benefit with combination therapy which is on the contrary of our findings, many studies [21-23], suggested that colistin based combination therapy is no more effective than colistin monotherapy for carbapenem-resistant A. baumannii which was against our findings in our trial.

Also CRE, p. aeruginosa and Klebsiella pneumoniae accounted for less than 25% of trial pathogens in AIDA[17], versus 33% in our study.

There was inconsistency in both studies as regard the impact of combination therapy on mortality when compared the AIDA trial to our trial. Both trials reported numerical reduction in 28 day mortality with combination therapy compared with colistin for CRE (80%, in colistin only group, versus 27% in combination group, and 35% versus 21%) in our study and AIDA trial respectively and in pseudomonas aeruginosa 100% versus 50% in combination therapy group, and 31% versus 25% in our study and AIDA trial respectively.

Also the incidence of acute kidney injury (AKI) in the combination therapy group was less than in the monotherapy group 24% versus 48% respectively.

The point of favor of our study as it is a prospective randomized trial for the treatment of XDR gram negative pathogens which is challenging in any clinical trial of pneumonia in critically ill patients diagnosing pneumonia and determining the influence of trial pathogen on outcomes.

Also our primary outcome of 28 day mortality is considered the gold standard end point for the treatment of severe infections in complex trial populations like our trial but mortality can be influenced by many variables unrelated to infection and treatment.

The dosage of meropenem in our study was 2000 mg every 8 hours as a 3 hour prolonged infusion like the recent guidance documents for resistant gram negative organisms for CRE when isolates have MICs to meropenem 8 mg/L or less[24-27].

CONCLUSIONS

The combination therapy of colistin plus meropenem affected the 28 day mortality, clinical cure and microbiological cure when compared to the colistin monotherapy.

Also affected the weaning of vasopressors, mechanical ventilation, improvement in all inflammatory markers & radiologically, all in favor of the combination therapy also the acute kidney injury incidence is lower in the combined colistin and meropenem group than the monotherapy.

Also further trials of combined colistin and meropenem is needed for CRE and pseudomonas aeruginosa given the numerical trends toward decreasing mortality in both our trial and AIDA.

Also as alternative treatment strategies, including the use of novel agents should be considered like noval B-lactam/ß-lactamase inhibitor combinations compared to colistin-based regimens for treating infections caused by these pathogens with improved efficacy and safety.

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