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Research Article

The Clinical Impacts of Adjunctive High Dose Meropenem Against Colistin-Sensitive/Carbapenem-Resistant Enetrobacteriaceae In Septic Critically Ill Patients

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Abstract: ***Background*:** Recently, sepsis associated with gram negative bacteria (GNB) have increased globally in critically ill patients in which infection by these GNB increases mortality, morbidity, and cost expenditure. A difficult to treat GNBs infections are belonged to multi-drug resistant MDR-Enterobacteriaceae.spp including CRE, since they are susceptible to a limited number of antibiotics. the importance to conserve colistin susceptibility by combination with other available antibiotics (ABs) is an imperative and of an urgent priority of our responsibility to mitigate the emerging of pan-resistant GNB (PR-GNB). The aim of this study is to compare efficacy outcomes of using colistin/high dose meropenem **[Group I]** with Colistin monotherapy **[Group II]** in critically ill patients who had sepsis caused by CRE regarding hemodynamics, infectious values, and overall major clinical outcomes in septic critically ill patients. ***Methods*:** We perform a retrospective analysis of 102 septic critically ill patients admitted to the adult ICU between April 2017 and April 2019. All patient's continuous variables were expressed as Mean ±SD by using the independent T-Test. Using of Chi Square test to express categorical variables, as numbers with percentages. ***Results*:** the mean overall age of 58.4±9.95 years. 56 subjects (54.90%) were male and 52 subjects (50.98%) were female. Objectively, the hemodynamic parameters were positively and significantly higher in Group I versus Group II. The %Δ CRP: ALB and (NE_{avg}) were in Group II significantly higher than Group I (269%±33%, and 7.12±0.19, 179%±30% and 6.05±0.07, respectively). The 28-day survival was significantly higher in Group I (48 (80.0%)) versus Group II (40 (64.5%)). In contrast, the ICU stay days, early, late, and 28-day mortality overall 28-day ICU mortality was higher in Group II versus Group I. ***Conclusion*:** In conclusion, our study has shown that colistin is more effective with a significant positive impact on clinical outcomes when used in combination with high dose meropenem extended infusion than colistin monotherapy in CRE septic critically ill patients. In case of CRE associated infections, It is highly advisable to use high dose meropenem extended infusion strategy if the MIC of meropenem not exceeds 16 mcg/ml even the sensitivity culture is resistant in vitro.

Keywords: Colistin, Critically ill patients, Gram negative bacteria, Meropenem, Mortality, Sepsis.

INTRODUCTION

Sepsis is a medical emergency that describes the body's systemic immunological response to an infectious process that can lead to end-stage organ dysfunction and death and remain one of the major causes of morbidity and mortality in critically ill patients (Gyawali, B. et al 2019; & Biancoa, G., & Boattinia, M. 2018).

The treatment of multidrug-resistant pathogens like Carbapenem-Resistant Enterobacteriaceae (CRE) infections in critically ill patients presents many challenges. Carbapenem-resistant Enterobacteriaceae (CRE) represents the most recent and worrisome evolution of the antibiotic resistance crisis. The mortality rate is highest among patients with blood stream infection (BSI). Since Invasive pathogens may acquire resistance genes which enable bacteria to produce enzymes like beta-lactamase and carbapenemase, express efflux systems, and modify the drug's target site and an alternative metabolic pathway. This has forced clinicians to consider treatment approaches based on combinations of drugs with impaired activity, and/or to rediscover drugs with suboptimal pharmacokinetics and toxicity issues. Ideally, a combination regimen should improve clinical success via improved reduction of the bacterial load, more rapid killing, killing or inhibition at lower drug

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concentrations, thus avoiding toxicity and minimising the risk of resistance selection (Bassetti, M. et al 2019; Paul, M. et al 2018; Fan, B. et al 2016; Sakoulas, G. 2017; & Dickstein, Y. et al).

Pharmacologically, Meropenem is a carbapenem antibiotic, showed in some studies a clinical activity against MDR-GNB including carbapenems when it infused at high dose over extended period as long as the minimum inhibitory concentration (MIC) of meropenem not exceeds 16 mcg/ml. Colistin, a polymyxin E antibiotic are bactericidal by inducing rapid cell death mediated through hydroxyl radical production which acts both by disrupting the cell membrane and by binding lipid polysaccharide and blocking the effects of endotoxin. it was first introduced in 1952 and was used routinely until the 1980 before it was abandoned for a period owing to its nephrotoxicity and neurotoxicity, is currently the most important available treatment option for these tenacious bacteria in septic critically ill patients (Xingchen Bian; Russo, A. et al 2018; Markou, N. et al 2003; Karabinis, A. et al 2004; Alhashem, F. et al 2017; & panel A.S). The aim of this study is to evaluate the clinical effect of adding high dose extended infusion of meropenem 2 g over 3 hours thrice daily to colistin (Group I) versus colistin monotherapy (Group II) in MDR-GNB infected septic critically ill patients regarding changes in hemodynamic indicators, changes in white blood cells and its differential ratios, changes in c-reactive protein to albumin ratio (Δ CRP:ALB), overall hospital length of stay (LOS), early, late, and overall mortalities.

METHODS AND MATERIALS

This was a single-center observational retrospective study conducted in the department of adult ICU of King Hussein Medical Hospital (KHMH) at Royal Medical Services (RMS) in Jordan between Apr 2017 to April 2019. this study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included 102 eligible critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problem. We excluded patients either were discharged, had carbapenem sensitivity, or died before completed at least 1 week after ICU admission or because the required data couldn't be recruited. Patients' demographics, diagnostics, anthropometrics, hemodynamic parameters of MAP and NE rate, empirical ABs for first 3 days of ICU admission, targeted ABs that were used after culture results, microbiological results, clinical and laboratory responses, colistin and meropenem renal adjusted doses, treatment durations, ICU LOS, and early, late, overall 28-day ICU mortality were recorded retrospectively through our institutional electronic medical records (Hakeem). All patient's continuous variables will be expressed as Mean±SD by using an Independent T-Test. Regarding categorical variables, Chi Square test will be used to express them as numbers with percentages.

RESULTS

In this study, we included 102 septic critically ill patients which admitted to our adult ICU with mean overall age of 58.4±9.95 years. 56 subjects (54.90%) were male and 52 subjects (50.98%) were female. This study we find the percentage changes of white blood cells, absolute neutrophil count, monocyte count, neutrophils to lymphocytes ratio, and monocytes to lymphocytes ratio (%ΔWBCs, %ΔANC, %ΔMC, %ΔNLR, and %ΔMLR, respectively) were significantly decreased after use high dose meropenem/colistin regimen. Also, the signs of systemic inflammatory response syndrome (SIRS) secondary to sepsis were clinically improved and the use of combination antibiotic regimens were infectiously considered more successful. The 28-day survival was significantly higher in antibiotic regimens that included high dose meropenem /colistin than in colistin alone. In contrast, the overall 28-day ICU mortality was higher in antibiotic regimens that included colistin alone than in high dose meropenem /colistin.

In our study the signs of sepsis that were included encompassed of hemodynamic parameters such as SBP_{avg}, DBP_{avg}, and MAP_{avg}, average norepinephrine infusion rate (NE_{avg}), percentage changes in albumin level (%ΔALB), percentage changes of c-reactive protein to albumin ratio (%ΔCRP: ALB), and average temperature (T_{avg}). %ΔWBCs, %ΔANC, %ΔMC, %ΔNLR, and %ΔMLR were significantly high in septic critically ill patients who were on antibiotic regimen that included colistin in combination with high dose meropenem (-43.2±%4%, -53.9%±5%, -61.8%±5%, -86.2%±8%, and -88.6%±7%, respectively) followed by meropenem (-17%±1.6%,-21.4%±2%,-34.8%±2%,58.9%±13%,-65.9%±11, respectively). These % Δ in complete blood counts were directly trended with %ΔALB and MAP_{avg} and inversely trended with %ΔCRP: ALB, NE_{avg}, and T_{avg}. The most significant %ΔALB and MAPavg were in Group I (Colistin+Meropenem) followed by Group II (Colistin), with Mean±SD of 29.3%±15% and 83.3±0.65 mmHg, 28.9%±14% and 76.2±1.15 mmHg, respectively. In contrast, the most significant %ΔCRP:ALB, NE_{avg}, and T_{avg} were in Group II followed by Group I, with Mean±SD of 269%±33%, 7.12±0.19 mcg/min, and 37.7±0.11 °C, 179%±30%, 6.54±0.17 mcg/min, 37.3±0.12 °C, 106±%11%, 6.05±0.07 mcg/min, and 36.9±0.06 °C, respectively. Also, the ICU and overall hospital stay days were significantly lowest in Group I (8.00±0.00 days and 9.00±0.00 days). Demographics, anthropometrics, laboratory data, hemodynamics, nutritional data, microbiological and antibiotic data, complete blood counts and percentages, clinical outcomes of the study's critically ill patients among the six tested groups are fully summarized in **Table 1-3**.

Table 1. Comparison of anthropometrics, laboratory data, hemodynamics, nutritional data, and clinical outcomes among the two tested groups

Variables		Group I (N=60)	Group II (N=62)	P-Value
Age (Yrs)		59.7±10.1	60.1±11.7	0.01 (S)
Sex	F	27 (50%)	25 (46.29%)	0.106 (NS)
	M	27 (50%)	29 (53.70%)	
BW (Kg)		72.3±8.84	75.9±10.2	0.07(NS)
BMI (Kg/m²)		25.7±3.74	25.9±3.81	0.11 (NS)
CRP_1 (mg/dl)		23.2±9.57	35.8±13.6	0.00 (S)
ALB_1 (g/dl)		2.65±0.18	2.77±0.28	0.00 (S)
CRP:ALB_1		7.09±3.06	10.8±5.12	0.00 (S)
CRP_{avg} (mg/dl)		5.07±2.77	7.61±2.87	0.00 (S)
ALB_{avg} (g/dl)		3.77±0.53	3.46±0.38	0.00 (S)
%ΔALB		29.3%±15%	28.9%±14%	0.00 (S)
CRP: ALB_{avg} (X: 1)		1.76±1.19	2.88±1.43	0.00 (S)
%ΔCRP:ALB		106±%11%	269%±33%	0.00 (S)
H.ALB_{avg} (g/day)		4.00±4.96	6.13±5.54	0.00 (S)
T_1 (°C)		37.5±0.06	38.2±0.11	0.00 (S)
T_{avg} (°C)		36.9±0.06	37.7±0.11	0.00 (S)
SBP_{avg} (mmHg)		113±0.65	106±1.15	0.00 (S)
DBP_{avg} (mmHg)		68.3±0.65	61.2±1.15	0.00 (S)
MAP_{avg} (mmHg)		83.3±0.65	76.2±1.15	0.00 (S)
HR_{avg} (bpm)		91.7±0.65	98.8±1.15	0.00 (S)
NE_{avg} (µg/min)		6.05±0.07	7.12±0.19	0.00(S)
TC_{avg} (Cal/day)		1302±283	1447±312	0.06 (NS)
PD_{avg} (g/100 Cal)		3.55±0.54	3.74±0.70	0.15 (NS)
HC	Positive	23 (42.59%)	31 (57.41%)	0.29 (NS)
	Negative	31 (57.41%)	23 (42.59%)	
Day(s) Pre-ICU		1.00±0.00	2.29±0.46	0.00 (S)
ICU Stay $day_{(s)}$		8.00±0.00	13.7±6.36	0.00 (S)
Hospital Stay day(s)		9.00±0.00	16.2±6.59	0.00 (S)
28-day ICU Survival		**48** (80.0%)	40 (64.5%)	0.00 (S)
28-day ICU MOR		12 (20.0%)	22 (35.5%)	
Early MOR (≤14 d)		**2** (3.33%)	**4** (6.45%)	
Late MOR (>14 d)		**10** (16.7%)	**18** (29.0%)	

Data are presented as either Mean±SD by using Independent T-Test or as number (%) by using chi square test (at p-value≤ 0.05).

Group I: Critically ill patients on Colistin+Meropenem.
Group II: Critically ill patients on Colistin monotherapy.
N: Number of studied critically ill patients.
BW: Body weight.
BMI: Body mass index.
CRP: C-reactive protein.
ALB: Albumin level.
CRP: ALB: C-reactive protein to albumin ratio.
H.ALB: Human albumin 20%.
T: Temperature.
HC: Hydrocortisone.
ICU: Intensive care unit.
F: Female.
M: Male.
1: Baseline after ICU admission.
2: After 1 week of ICU admission.
Avg: Average value through first week of ICU admission.
SBP: Systolic blood pressure.
DBP: Diastolic blood pressure.
MAP: Mean arterial pressure.
HR: Heart rate.
NE: Norepinephrine.
TC: Total calories.
Cal: Kcalories.
PD: Protein density.
MOR: Mortality.

Table 2. Comparison of complete blood counts and percentages among the two tested groups

Variables	Group I (N=60)	Group II (N=62)	P-Value
$WBCs_1$ ($\times10^3$Cells/µl)	14.1±1.49	17.9±1.43	0.00(S)
ANC_1 ($\times10^3$Cells/µl)	11.1±1.55	14.7±1.75	0.00 (S)
$\%Neut_1$	78.4%±4.0%	81.7%±4.9%	0.00(S)
MC_1 ($\times10^3$ Cells/µl)	1.42±1.99	1886±0.26	0.00 (S)
$\%M_1$	10.1%±0.5%	10.5%±0.6%	0.00 (S)
TLC_1 ($\times10^3$ Cells/µl)	0.74±0.50	1.18±0.73	0.00(S)
$\%Lym_1$	5.2%±3.6%	6.6%±4.3%	0.03 (S)
NLR_1 (X:1)	24.7±27.9	19.7±18.9	0.02 (S)
MLR_1 (X:1)	3.17±3.59	2.52±2.43	0.02 (S)
$WBCs_2$ ($\times10^3$ Cells/µl)	8.07±1.30	14.9±1.28	0.00 (S)
ANC_2 ($\times10^3$ Cells/µl)	5.14±1.15	11.6±1.49	0.00(S)
$\%Neut_2$	63.3%±4.3%	77.5%±4.8%	0.00(S)
MC_2 ($\times10^3$ Cells/µl)	0.55±0.12	1.23±0.16	0.00 (S)
$\%M_2$	6.7%±0.5%	8.2%±0.5%	0.00 (S)
TLC_2 ($\times10^3$ Cells/µl)	2.38±0.29	2.09±0.72	0.00 (S)
$\%Lym_2$	29.9%±4.7%	14.3%±5.3%	0.00 (S)
NLR_2 (X:1)	2.19±0.56	6.31±2.58	0.00 (S)
MLR_2 (X:1)	0.23±0.06	0.67±0.27	0.00 (S)
%ΔWBCs	-43.2±%4%	-17%±1.6%	0.00 (S)
%ΔANC	-53.9%±5%	-21.4%±2%	0.00 (S)
%ΔMC	-61.8%±5%	-34.8%±2%	0.00 (S)
%ΔTLC	386%±449%	120%±105%	0.00 (S)
%ΔNLR	-86.2%±8%	-58.9%±13%	0.00 (S)
%ΔMLR	-88.6%±7%	-65.9%±11%	0.00 (S)

Data are presented as either Mean±SD by using Independent T-Test or as number (%) by using chi square test (at p-value≤ 0.05).

Group I: Critically ill patients on Colistin+Meropenem.
Group II: Critically ill patients on Colistin monotherapy.
N: Number of studied critically ill patients.
1: Baseline after ICU admission.
2: After 1 week of ICU admission.

Avg: Average value through first week of ICU admission.
WBCs: White blood cells.
ANC: Absolute neutrophil count.
Neut: Neutrophils.
MC: Monocyte count.
TLC: Total lymphocyte count.
Lym: Lymphocytes.
NLR: Neutrophil to lymphocyte ratio.
MLR: Monocyte to lymphocyte ratio.

Table 3. Comparison of microbiological and antibiotic data among the tested groups

Variables		Group I (N=60)	Group II (N=62)	P-Value
EMP ABs 1st 3-4 days	CFP	10 (16.7%)	12 (19.4%)	0.110 (NS)
	PIP/TAZ	24 (40.0%)	18 (29.0%)	
	MER	12 (20.0%)	18 (29.0%)	
	IMP/CIL	14 (23.3%)	14 (22.6%)	
CrCl (ml/min)		64.6±20.3	30.8±10.9	0.00 (S)
Meropenem (mg/day)		5778±634	0.00±0.00	0.00(S)
Colistin (MIU/day)		9.94±2.65	6.05±1.08	0.00(S)
MDR-GNB	MDR-A.B	2(3.3%)	10(16.1%)	0.00(S)
	CRE-E.Coli	8(13.3%)	4(6.5%)	
	CRE-K.P	14(23.3%)	6(9.7%)	
	CRE-E.spp	8(13.3%)	12(19.4%)	
	CRE-S.M	8(13.3%)	6(9.7%)	
	CRE-P.spp	8(13.3%)	6(9.7%)	
	CRE-C.spp	2(3.3%)	10(16.1%)	
	MDR-P.A	10(16.7%)	8(12.9%)	

Data are presented as either Mean±SD by using Independent T-Test or as number (%) by using chi square test (at p-value≤ 0.05).

Group I: Critically ill patients on Colistin+Meropenem.
Group II: Critically ill patients on Colistin monotherapy.
N: Number of studied critically ill patients.
1: Baseline after ICU admission.
2: After 1 week of ICU admission.
MDR: Multidrug-resistant.
HC: Hydrocortisone.
AB: Antibiotics.
CrCl: Creatinine clearance.
MIU: Millimillion unit.

CRE: Carbapenem-resistant *Enterobacteriaceae.*
A.B: Acinetobacter.Baumannii.
E.Coli: Escherichia.Coli.
K.P: Klebsiella. Pneumonia.
E.spp: Enterobacter.Species.
S.M: Serratia.Marcescens.
P.spp: Providencia.species.
C.spp: Citrobacter.species.
P.A: Pseudomonas.Aeruginosa.
EMP: Empirical antibiotics.
CEP: Cefepime.
PIP/TAZ: Piperacillin/Tazobactam.
MER: Meropenem.
IMP/CIL: Imipenem/Cilastatin.

DISCUSSION

Recently, a few studies compared the clinical outcomes and effectiveness between colistin combination and monotherapy in septic critically ill patients. But what is unique in This study we analyzed and compared the clinical features and outcome of used the dual-antibiotic regimens that included colistin in combination with meropenem versus the mono-antibiotic regimens. In our study, we additionally tested three major principles in infectious diseases of sepsis; first one is when used Colistin in combination with other antibiotic to increase the rate of eradication and to lower risk of emerging resistant in critically ill patients. Secondly, adding antibiotic in high dose, extended infusion rate regardless of culture sensitivity result like carbapenems including meropenem may be effective in vivo though its resistant in vitro if the MIC of meropenem not exceeds 16 mcg/ml when used maximum dose and infused over at least 3 hours per dose. Thirdly, we took into consideration the nutritional impacts of lowering lymphocyte count and corticosteroid impacts on elevation neutrophil and lowering lymphocyte counts. In this study, the total calorie intake, protein density intake, and hydrocortisone -commonly used in refractory septic shock patients- doses of 200 mg/day were insignificantly different among the two groups, which precluded their exaggerated confounding effects on NLR and MLR. In this study, we investigated the confounding impacts of empirical ABs of cefepime, piperacillin/tazobactam, meropenem standard infusion (over 30 minutes), and imipenem/cilastatin before commencing our tested targeted ABs of colistin, and meropenem extended infusion (over 3 hours) which were also insignificant. In this study, meropenem high dose was 2 g infused over 3 hours every 8 hours. The mean meropenem renal adjusted doses used was 5778±634 mg/day for Group I, in which the total daily dose of meropenem was divided into three doses each infused over 3 hours. The mean colistin renal adjusted doses used were 9.94±2.65 MIU/day for Group I, and 6.05±1.08 MIU/day for Group II.

Our data shown there are strong correlations between CRP and ALB levels that were in septic patients the ALB level decreased through escaping from the intravascular compartment to interstitial compartment which are directly related to the CRP level and subsequently to exotoxin that are released from GNB. We find the positive correlation between CRP and ALB explains the direct trended in %ΔALB, MAP_{avg} and inverse trended in %ΔCRP:ALB, NE_{avg}, and T_{avg} to clinical improvement in sepsis as manifested by significantly decreasing in %ΔWBCs, %ΔANC, %ΔMC, %ΔNLR, and %ΔMLR among the six tested groups in following order Group I>Group II. This study shows some limitations that should be acknowledged. First, the study was performed in a single center, and the results might not be generalizable to other institutions. Second, the observational nature of the study brings about an intrinsic limitation in the analysis. Third, the number of patients is relatively low, and further multicenter prospective studies are needed to confirm our findings. Finally, the underlying mechanisms of resistance in MDR-GNBs were not routinely assessed in our population. However, this is a real-life clinical experience providing useful suggestions to clinicians about the management of difficult-to-treat and poorly studied infections.

CONCLUSION

In conclusion, our data showed the clinical features and the high rates of mortality in ICU patients with septic shock due to MDR infections in colistin monotherapy compared to colistin combination with high dose meropenem, even if carbapenems antibiotic are resistant in sensitivity culture results. All these findings suggest that the synergistic effect of high dose meropenem extended infusion for the treatment of ICU patients with MDR infection, which it is decrease colistin nephrotoxicity, colistin resistant and improve clinical outcomes, and reduce mortality and length of stay in ICU unit or in hospital. , It is advisable to use high dose meropenem extended infusion strategy as a pharmacodynamic booster agents with the renal

adjusted colistin in septic critically ill patients with MDR-GNB.

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