International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Synergistic Activity Comparison between Colistin/Tigecycline and Colistin/High Dose Meropenem against Carbapenem Resistant Enetrobacteriaceae in Critically Ill Patients with Ventilator Associated Pneumoniae

Sahar .I. Al-Niemat; Ph[1], "Moh'd Nour" Mahmoud Bani Younes; Ph[1], Jaafar Abd Alrahman Abu Abeeleh; Ph[1], Amani Daoud Alshawabkeh; PharmD[1]
[1]Clinical Pharmacy Department/King Hussein Medical Hospital/Royal Medical Services/Amman/Jordan

Address correspondence to: "Moh'd Nour" Bani Younes, Clinical Pharmacy Specialist, MSc Clinical Pharmacy, BCPS, BCCCP, BCNSP, BCACP, BCIDP, Chief of EN and TPN Unit, King Hussein Medical Hospital, King Abdullah II St 230, Amman 11733, Jordanian Royal Medical Services, e-mail: panasomycine @ hotmail.com.

Abstract— Background*: Universally, A very difficult to-treat gram negative bacteria, including but not excluded to carbapenem-resistant enterobacteriaceae (CRE), are increasing rapidly. With the shortages of the newer anti-CRE antibiotics in our country, CRE-associated pneumonia and sepsis management are primarily restricted to colistin. Therefore in this study, we primarily tested the adjunctive clinical impacts of tigecycline (Group I) compared with high dose extended infusion meropenem (Group II) regarding hemodynamics, infectious values, and overall major clinical outcomes in mechanically ventilated critically ill patients.* ***Methods****: We perform a retrospective analysis of 114 eligible 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. Regarding categorical variables, Chi Square test was used to express them as numbers with percentages.* ***Results****: The mean overall age was 58.4±9.95 years. 53 subjects (46.49%) were female and 61 subjects (53.51%) were male. The 28-day survival was significantly higher in Group I (50 (92.6%)) than Group II (48 (80.0%)). Objectively, the hemodynamic parameters were positively and significantly higher in Group I versus Group II. Group I had a significantly higher %ΔALB and significantly lower %ΔCRP:ALB compared with Group II (32.6%±15% vs 28.8%±15% and 71.9%±16% vs 286%±301%, respectively). Also, the ICU stay days and mortalities were significantly decreased in Group I compared with Group II with ICU stay days, early, late, and 28-day mortality were 7.93±0.26 days, 2 (3.7%), 2 (3.7%), and 4 (7.4%) vs 11.8±5.5 days, 2 (3.33%), 10 (16.7%), and 12 (20.0%).* ***Conclusion****: In conclusion, the present study has shown that colistin is more effective with a significant positive impacts on clinical outcomes when used in combination with standard dose of tigecycline than high dose meropenem extended infusion in CRE associated pneumonia and septic critically ill patients. In case of CRE associated infections, It is highly advisable to use tigecycline or at least high dose meropenem extended infusion strategy as a pharmacodynamic booster agents with the renal adjusted colistin.*

Keywords— *Carbapenem Resistant Enterobacteriaceae, Colistin, Critically ill patients, High dose meropenem, Tigecycline, Ventilator associated pneumonia.*

I. INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the most common complications in the process of mechanical ventilation (MV), which seriously affects the prognosis of critically ill patients. The spread of antimicrobial resistance by carbapenemase-producing Enterobacteriaceae (CPE) has taken global dimensions at an alarmingly fast pace, posing a major public health threat. [1] Enterobacteriaceae, a family of enteric gram-negative bacteria (GNB) responsible for a variety of community and healthcare-acquired infections.[2] Infections caused by multidrug-resistant pathogens like Carbapenem-Resistant Enterobacteriaceae (CRE), which are associated with high rate of morbidity and mortality and extremely limited therapeutic options to treat it. [3-4]

Treatment options for CRE are limited and include combinations of tigecycline, aminoglycosides, carbapenems or polymyxins as Colistin which is a polypeptide antibiotic of the polymyxin family that causes rapid bacterial killing in a concentration-dependent manner. It acts primarily on the Gram-negative bacterial cell wall, leading to rapid permeability changes in the cytoplasmic membrane and ultimately to cell death. colistin monotherapy is considered to have limited efficacy against infections caused by (CRE) and high rates of mortality in patients infected with this pathogen [5-7]

Phenotypic resistance to carbapenems is typically caused by two main mechanisms: (1) β-lactamase activity combined with structural mutations that resulted in CRE with moderately elevated in MIC and (2) Exclusive production of carbapenemases enzymes that resulted in CPE with high elevated in MIC. The former mechanism includes extended-spectrum β-lactamases (ESBLs) and AmpC cephalosporinases (AmpC), for which expression in enterobacteriaceae is most

Sahar .I. Al-Niemat; Ph, "Moh'd Nour" Mahmoud Bani Younes; Ph, Jaafar Abd Alrahman Abu Abeeleh; Ph, and Amani Daoud Alshawabkeh; PharmD, "Synergistic Activity Comparison between Colistin/Tigecycline and Colistin/High Dose Meropenem against Carbapenem Resistant Enetrobacteriaceae in Critically Ill Patients with Ventilator Associated Pneumoniae," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 3, Issue 3, pp. 28-32, 2020.

often associated with hyperproduction of enzymes accompanied with other mechanism of resistants. [8-9]

Tigecycline is associated with excess deaths and treatment failure, when used as monotherapy. Most experts have recommended that tigecycline be avoided for the treatment of severe infections and that it should be reserved for use as a last-resort drug; despite these limitations, tigecycline is a useful alternative for the treatment of infections due to multidrug-resistant (MDR) GNB, such as CRE and CPE. Pharmacologically, tigecycline is non-nephrotoxic nature compared to other potentially active antimicrobial agents for CRE, such as polymyxins and aminoglycosides. A high-dose colistin regimen has been used against CRE infection so when use in combination no need for high dose of colistin to control CRE infection so decrease the nephrotoxicity effect of it. [10-13] The aim of this study is to compare the proposed synergistic clinical usefulness of adding standard dose of tigecycline at dose regimen of 100 mg followed by 50 mg twice daily (Group I) versus adding high dose extended infusion of meropenem 2 g over 3 hours thrice daily (Group II) to the renal dose adjusted colistimethate sodium in CRE infected critically ill patients regarding changes in white blood cells and its differential ratios, changes in hemodynamic indicators, changes in c-reactive protein to albumin ratio (Δ CRP:ALB), overall hospital length of stay (LOS), early, late, and overall mortalities.

II. 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 114 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. Totally, 1007 ICU patients were excluded because they either discharged, had carbapenem sensitivity, or died before completed at least 1 week after ICU admission (687 participants) or because the required data couldn't be recruited (320 participants). Patients' demographics, diagnostics, anthropometrics, hemodynamic parameters, 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).

We perform a retrospective analysis of patients admitted to the adult ICU between April 2017 and April 2019 who were their baseline and follow-up data of vital signs, WBCs with differential, CRP and ALB, LOS, and date of discharging or dying could be obtained. Patients will be excluded if they discharged or died before completed first week of ICU admission and had sensitivity to all available anti-pseudomonal β-lactam ABs in our institution. All patient's continuous variables will be expressed as Mean ±SD and their differences between the two tested groups as Mean ±SD by using the independent and dependent T-Test, respectively. Regarding categorical variables, Chi Square test will be used to express them as numbers with percentages.

VAP was defined as "a new or progressive pulmonary infiltration occurring >48hours after receiving invasive MV or within 48hours after extubation, plus at least 2 of the following: temperature >38.0 or <36.0°C; leukocytosis or leukopenia; and purulent tracheal secretions or sputum. [14] All patient's continuous variables will be expressed as Mean±SD and their differences between the two tested groups as Mean±SEM by using the independent and dependent T-Test, respectively. Regarding categorical variables, Chi Square test will be used to express them as numbers with percentages. All statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA); P-values ≤0.05 were considered statistically significant.

III. Results

The study included 114 septic mechanically ventilated critically ill patients admitted to our adult ICU with mean overall age of 58.4±9.95 years. 53 subjects (46.49%) were female and 61 subjects (53.51%) were male. The 28-day survival was significantly higher in Group I critically ill patients that included tigecycline standard regimen dose as an adjunctive to the targeted colistin treatment (50 (92.6%)) than Group II (critically ill patients that in contrast included high dose meropenem extended infusion antibiotic (48 (80.0%)). Objectively, the hemodynamic parameters were positively and significantly higher in Group I versus Group II in which the Mean±SD of average systolic blood pressure (SBP_{avg}), average diastolic blood pressure (DBP_{avg}), and average mean arterial pressure (MAP_{avg}) were 115±0.66 mmHg, 69.9±0.66 mmHg, and 84.9±0.66 mmHg vs 106±12.8 mmHg, 60.9±11.5 mmHg, and 75.8±11.9 mmHg, subsequently. Regarding nutritional risk indices of %Δ of c-reactive protein (%ΔCRP), albumin level (%ΔALB), and CRP to ALB ratio (%ΔCRP:ALB), Group I had a significantly higher %ΔALB and significantly lower %ΔCRP:ALB compared with Group II (32.6%±15% vs 28.8%±15% and 71.9%±16% vs 286%±301%, respectively).

Infectiously, %Δ of total white blood cells (%ΔWBCs), neutrophil count (%ΔANC), monocyte count (%ΔMC), ANC to TLC ratio (%ΔNLR), and MC to TLC ratio (%Δ MLR) were significantly decreased after adding adjunctive tigecycline compared with adjunctive extended infusion meropenem in which the Mean±SD for aforementioned infectious parameters in Group I versus Group II were -61.0%±9%, -76.5%±9%, -80.5%±8%, -91%±11%, and -92.3%±9% vs -43.2±%4%, -53.9%±5%, -61.8%±5%, -86.2%±8%, and -88.6%±7%, respectively. Also, the ICU stay days and mortalities were significantly decreased in Group compared with Group II septic critically ill patients with ICU stay days, early, late, and 28-day mortality were 7.93±0.26 days, 2 (3.7%), 2 (3.7%), and 4 (7.4%) vs 11.8±5.5 days, 2 (3.33%), 10 (16.7%), and 12 (20.0%). Demographics, anthropometrics, laboratory data, hemodynamics, nutritional data, microbiological and antibiotic data, complete blood

Sahar .I. Al-Niemat; Ph, "Moh'd Nour" Mahmoud Bani Younes; Ph, Jaafar Abd Alrahman Abu Abeeleh; Ph, and Amani Daoud Alshawabkeh; PharmD, "Synergistic Activity Comparison between Colistin/Tigecycline and Colistin/High Dose Meropenem against Carbapenem Resistant Enetrobacteriaceae in Critically Ill Patients with Ventilator Associated Pneumoniae," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 3, Issue 3, pp. 28-32, 2020.

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 tested groups.

Variables		Total (N=114)	Group I (N=54)	Group II (N=60)	P-Value
Age (Yrs)		58.4±9.95	56.6±8.13	59.7±10.1	0.01 (S)
Sex	F	53 (46.49%)	26 (48.15%)	27 (45%)	0.106 (NS)
	M	61 (53.51%)	28 (51.85%)	33 (55%)	
BW (Kg)		73.9±9.32	74.2±10.2	72.3±8.84	0.07(NS)
BMI (Kg/m²)		25.7±3.74	25.9±3.99	25.3±3.26	0.11 (NS)
CRP_1 (mg/dl)		23.2±9.57	34.2±17.9	19.7±5.21	0.00 (S)
ALB_1 (g/dl)		2.65±0.18	2.75±0.32	2.63±0.16	0.00 (S)
$CRP:ALB_1$		7.09±3.06	10.24±5.90	5.99±1.85	0.00 (S)
CRP_{avg} (mg/dl)		7.94±3.11	5.07±2.77	8.73±2.19	0.00 (S)
ALB_{avg} (g/dl)		3.42±0.38	3.77±0.53	3.34±0.28	0.00 (S)
%ΔALB		29.3%±15%	32.6%±15%	28.8%±15%	0.00 (S)
$CRP: ALB_{avg}$ (X: 1)		3.04±1.49	1.76±1.19	3.38±1.09	0.00 (S)
%ΔCRP:ALB		106±%11%	71.9%±16%	286%±301%	0.00 (S)
T_1 (°C)		37.3±0.07	38.2±1.28	37.5±0.06	0.00 (S)
T_{avg} (°C)		36.9±0.06	36.8±0.07	37.7±1.28	0.00 (S)
SBP_{avg} (mmHg)		113±0.65	115±0.66	106±12.8	0.00 (S)
DBP_{avg} (mmHg)		68.3±0.65	69.9±0.66	60.9±11.5	0.00 (S)
MAP_{avg} (mmHg)		83.3±0.65	84.9±0.66	75.8±11.9	0.00 (S)
HR_{avg} (bpm)		91.7±0.65	90.1±0.66	99.3±12.8	0.00 (S)
NE_{avg} (µg/min)		6.05±0.07	5.86±0.08	7.99±5.72	0.00(S)
TC_{avg} (Cal/day)		1402±274	1420±175	1302±283	0.06 (NS)
PD_{avg} (g/100 Cal)		3.57±0.70	3.71±0.72	3.55±0.54	0.15 (NS)
HC	Positive	45 (43.86%)	22 (40.74%)	23 (38.33%)	0.29 (NS)
	Negative	69 (60.53%)	32 (59.26%)	37 (61.17%)	
ICU Stay $day_{(s)}$		9.87±0.00	7.93±0.26	11.8±5.5	0.00 (S)
Hospital Stay day(s)		9.00±0.00	8.19±0.39	11.2±3.12	0.00 (S)
28-day ICU Survival		98 (85.96%)	50 (92.6%)	48 (80.0%)	0.00 (S)
28-day ICU MOR		16 (14.04%)	4 (7.4%)	12 (20.0%)	
Early MOR (≤14 d)		4 (3.51%)	2 (3.7%)	2 (3.33%)	
Late MOR (>14 d)		12 (10.53%)	2 (3.7%)	10 (16.7%)	

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+Tigecycline.
Group II: Critically ill patients on Colistin+Meropenem.
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 tested groups.

Variables	Total (N=114)	Group I (N=54)	Group II (N=60)	P-Value
$WBCs_1$ (×10^3Cells/µl)	13.8±7.29	13.3±1.09	14.1±1.49	0.00(S)
ANC_1 (×10^3Cells/µl)	10.9±7.94	10.1±1.15	11.1±1.55	0.00 (S)
$\%Neut_1$	78.8%±7.7%	75.8%±4.8%	78.4%±4.0%	0.00(S)
MC_1 (×10^3 Cells/µl)	1.39±1.02	1.29±1.48	1.42±1.99	0.00 (S)
$\%M_1$	9.8%±0.9%	9.7%±0.6%	10.1%±0.5%	0.00 (S)
TLC_1 (×10^3 Cells/µl)	0.81±0.89	0.84±0.62	0.74±0.50	0.00(S)
$\%Lym_1$	6.12%±4.2%	6.4%±4.8%	5.2%±3.6%	0.03 (S)
NLR_1 (X:1)	22.2±12.2	21.3±16.5	24.7±27.9	0.02 (S)
MLR_1 (X:1)	2.87±2.6	2.73±2.11	3.17±3.59	0.02 (S)
$WBCs_2$ (×10^3 Cells/µl)	4.404±3.79	2.01±2.42	8.07±1.30	0.00 (S)
ANC_2 (×10^3 Cells/µl)	2.41±1.19	2.38±0.99	5.14±1.15	0.00(S)
$\%Neut_2$	51.1%±16%	44.2%±15%	63.3%±4.3%	0.00(S)
MC_2 (×10^3 Cells/µl)	0.32±0.98	0.25±0.11	0.55±0.12	0.00 (S)
$\%M_2$	5.56%±1.8%	4.7%±1.6%	6.7%±0.5%	0.00 (S)
TLC_2 (×10^3 Cells/µl)	2.36±1.56	2.46±0.46	2.38±0.29	0.00 (S)
$\%Lym_2$	36.7%±17%	49.8%±16%	29.9%±4.7%	0.00 (S)

Sahar .I. Al-Niemat; Ph, "Moh'd Nour" Mahmoud Bani Younes; Ph, Jaafar Abd Alrahman Abu Abeeleh; Ph, and Amani Daoud Alshawabkeh; PharmD, "Synergistic Activity Comparison between Colistin/Tigecycline and Colistin/High Dose Meropenem against Carbapenem Resistant Enetrobacteriaceae in Critically Ill Patients with Ventilator Associated Pneumoniae," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 3, Issue 3, pp. 28-32, 2020.

NLR_2 (X:1)	**1.69±14.5**	**1.03±0.51**	**2.19±0.56**	**0.00 (S)**
MLR_2 (X:1)	**0.18±0.55**	**0.11±0.05**	**0.23±0.06**	**0.00 (S)**
%ΔWBCs	**-58.8%±19%**	**-61.0%±9%**	**-43.2±%4%**	**0.00 (S)**
%ΔANC	**-65.9%±24%**	**-76.5%±9%**	**-53.9%±5%**	**0.00 (S)**
%ΔMC	**-71.9%±20%**	**-80.5%±8%**	**-61.8%±5%**	**0.00 (S)**
%ΔTLC	**389%±526%**	**398%±371%**	**386%±449%**	**0.00 (S)**
%ΔNLR	**-89.9%±80%**	**-91%±11%**	**-86.2%±8%**	**0.00 (S)**
%ΔMLR	**-90.4%±66%**	**-92.3%±9%**	**-88.6%±7%**	**0.00 (S)**
Data are presented as either Mean±SD by using independent T-test test or as number (%) by using chi square test (at p-value≤ 0.05).				
Group I: Critically ill patients on Colistin+Tigecycline. **Group II: Critically ill patients on Colistin+Meropenem.** **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		Total (N=114)	Group I (N=54)	Group II (N=60)	P-Value
EMP ABs 1st 3-4 days	**CFP**	**24 (21.1%)**	**14 (25.9%)**	**10 (16.7%)**	**0.110 (NS)**
	PIP/TAZ	**24 (21.1%)**	**10 (18.5%)**	**24 (40.0%)**	
	MER	**22 (19.3%)**	**10 (18.5%)**	**12 (20.0%)**	
	IMP/CIL	**34 (29.8%)**	**20 (37.0%)**	**14 (23.3%)**	
CrCl (ml/min)		**81.3±44.64**	**103±75.9**	**64.6±20.3**	**0.00 (S)**
Meropenem (mg/day)		**2889±317**	**0.00±0.00**	**5778±634**	**0.00(S)**
Colistin (MIU/day)		**10.2±4.93**	**10.9±2.06**	**9.94±2.65**	**0.00(S)**
MDR-GNB	**MDR-A.B**	**12 (10.5%)**	**10 (18.5%)**	**2 (3.3%)**	**0.00(S)**
	CRE-E.Coli	**10 (8.78%)**	**2 (3.7%)**	**8 (13.3%)**	
	CRE-K.P	**20 (17.5%)**	**6 (11.1%)**	**14 (23.3%)**	
	CRE-E.spp	**14 (12.3%)**	**6 (11.1%)**	**8 (13.3%)**	
	CRE-S.M	**16 (14.03%)**	**8 (14.8%)**	**8 (13.3%)**	
	CRE-P.spp	**12 (10.5%)**	**4 (7.4%)**	**8 (13.3%)**	
	CRE-C.spp	**12 (10.5%)**	**10 (18.5%)**	**2 (3.3%)**	
	MDR-P.A	**18 (15.8%)**	**8 (14.8%)**	**10 (16.7%)**	

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+Tigecycline.
Group II: Critically ill patients on Colistin+Meropenem.
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.

IV. DISCUSSION

A very limited studies compared the clinical outcomes and effectiveness between colistin combinations with either tigecycline versus meropenem in septic critically ill patients. In this study, we additionally tested the pharmacodynamic potentiation effects of tigecycline and high dose extended infusion meropenem in mitigation the pharmacokinetics/pharmacodynamics drawbacks of colistin therapy for critically ill patients with septic shock. [15] Colistin, a polymyxin E antibiotic which 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 only available treatment option for these tenacious bacteria in septic mechanically ventilated critically ill patients in our intensive care unit (ICU). [16] In case of globally increasing prevalence of MDR Escherichia.Coli (E.Coli), Klebsiella. Pneumonia (K.P), Enterobacter.Species (E.spp), Serratia.Marcescens (S.M), Providencia.species (P.spp), and Citrobacter.species (C.spp) in critically ill patients with long ventilation days (VDs), 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). [17-20] The uniqueness of our study is that we compared the two dual colistin combinations with each other in mechanically ventilated septic critically ill patients.

Sahar .I. Al-Niemat; Ph, "Moh'd Nour" Mahmoud Bani Younes; Ph, Jaafar Abd Alrahman Abu Abeeleh; Ph, and Amani Daoud Alshawabkeh; PharmD, "Synergistic Activity Comparison between Colistin/Tigecycline and Colistin/High Dose Meropenem against Carbapenem Resistant Enetrobacteriaceae in Critically Ill Patients with Ventilator Associated Pneumoniae," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 3, Issue 3, pp. 28-32, 2020.

The nutritional and steroidal impacts of severe wasting and hydrocortisone therapy on overestimation of NLR in our study's patients were also taking into consideration in which the total calorie (TC) inputs, protein density inputs, and hydrocortisone replacement doses of 200 mg/day were insignificantly different among the two groups. The confounding effects of empirical antibiotics that were used during first 3 days of ICU admission were also insignificant between the compared groups. The mean colistin and meropenem renal adjusted doses used in this study was 10.9±2.06 MIU/day and 0 mg/day for Group I versus 9.94±2.65 MIU/day and 5778±634 mg/day for Group II, respectively. The tigecycline which is a broad spectrum antibiotic with high volume of distribution, might be an alternative worth considering in septic critically ill patients as an adjunctive treatment to other bactericidal antibiotics such as colistin and newer non-β lactam β-lactamases inhibitors/β-lactam ABs such as meropenem/vaborbactam and ceftazidime/avibactam.

V. CONCLUSION

In conclusion, the present study has shown that colistin is more effective with a significant positive impacts on clinical outcomes when used in combination with standard dose of tigecycline than high dose meropenem extended infusion in CRE associated septic critically ill patients. In case of CRE associated sepsis, It is highly advisable to use tigecycline at dose of 50 mg BID after 100 mg loading dose or at least high dose meropenem extended infusion strategy as a pharmacodynamic booster agents with the renal adjusted colistin. This study is limited by its retrospective design, using single-center data including only ICU patients, and an overall lack of robust clinical data. Nonetheless, our center is an experienced and high-volume unit, so our data may be useful in other centers. A larger, multisite, and prospective study is needed to control for multiple confounders.

REFERENCES

[1] Geladari A, Simitsopoulou M, Antachopoulos C, Roilides E. Dose-Dependent Synergistic Interactions of Colistin with Rifampin, Meropenem, and Tigecycline against Carbapenem-Resistant Klebsiella pneumoniae Biofilms. Antimicrob Agents Chemother. 2019;63(3):e02357-18. Published 2019 Feb 26. doi:10.1128/AAC.02357-18.

[2] Logan LK, Weinstein RA. 2017. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis 215:S28–S36. doi:10.1093/infdis/jiw282.

[3] T. Amat1, T. AmatEmail the author T. Amat, A. Gutiérrez-Pizarraya,Machuca, I. Gracia-Ahufinger, E. Pérez-Nadales, Á. Torre-Giménez, J. Garnacho-Montero, J.M. Cisneros, J. Torre-Cisneros,Editor: M. Paul. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant Acinetobacter baumannii.CMI. Volume 24, Issue 6, Pages 630–634.

[4] Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR. Infections Caused by Carbapenem-Resistant Enterobacteriaceae: An Update on Therapeutic Options. Front Microbiol. 2019;10:80. Published 2019 Jan 30. doi:10.3389/fmicb.2019.00080

[5] Kuti JL, Kim A, Cloutier DJ, Nicolau DP. Evaluation of Plazomicin, Tigecycline, and Meropenem Pharmacodynamic Exposure against Carbapenem-Resistant Enterobacteriaceae in Patients with Bloodstream Infection or Hospital-Acquired/Ventilator-Associated Pneumonia from the CARE Study (ACHN-490-007). Infect Dis Ther. 2019;8(3):383–396. doi:10.1007/s40121-019-0251-4.

[6] Chen Z, Shi X. Adverse events of high-dose tigecycline in the treatment of ventilator-associated pneumonia due to multidrug-resistant pathogens. *Medicine (Baltimore)*. 2018;97(38):e12467. doi:10.1097/MD.0000000000012467

[7] Zihan Chen, MD and Xiaoyan Shi, MD, PhD . Adverse events of high-dose tigecycline in the treatment of ventilator-associated pneumonia due to multidrug-resistant pathogens. Medicine (Baltimore) ,v.97(38); 2018 Sep,PMC6160260.

[8] Shio-Shin Jean, Nan-Yao Lee, Hung-Jen Tang,, Min-Chi Lu, Wen-Chien Ko and Po-Ren Hsueh. Carbapenem-Resistant Enterobacteriaceae Infections: Taiwan Aspects. Microbiol., 27 November 2018 | https://doi.org/10.3389/fmicb.2018.02888.

[9] Ghasemian, Abdolmajida,b; Shafiei, Morvaridd; Hasanvand, Fatemehc; Shokouhi Mostafavi, Seyyed K.c. Carbapenem and colistin resistance in Enterobacteriaceae: worldwide spread and future perspectives. Reviews in Medical Microbiology: October 2018 - Volume 29 - Issue 4 - p 173-176 ,doi: 10.1097/MRM.0000000000000142.

[10] Yohei Doi. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections Clinical Infectious Diseases, Volume 69, Issue Supplement_7, 1 December 2019, Pages S565–S575.

[11] E. Durante-Mangoni, R. Andini, R. Zampino. Management of carbapenem-resistant Enterobacteriaceae infections. European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier 1198-743X/© 2019 .

[12] Michele Yamamoto & Aurora E Pop-Vicas .Treatment for infections with carbapenem-resistant Enterobacteriaceae: what options do we still have?Critical Care volume 18, Article number: 229 (2014).

[13] Jesús Rodríguez-Baño,a Belén Gutiérrez-Gutiérrez,a Isabel Machuca,b Alvaro Pascuala. Treatment of Infections Caused by Extended-Spectrum-BetaLactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clinical Microbiology Reviews .April 2018 Volume 31 Issue 2 e00079-17 .

[14] Chen, Zihan MD; Shi, Xiaoyan MD, PhD*Section Editor(s): Bellou., Abdelouahab. Adverse events of high-dose tigecycline in the treatment of ventilator-associated pneumonia due to multidrug-resistant pathogens. Medicine: September 2018 - Volume 97 - Issue 38 - p e12467doi: 10.1097/MD.0000000000012467.

[15] Dijkmans AC , Wilms EB , Kamerling IM , Birkhoff W , Ortiz-Zacarías NV , van Nieuwkoop C , Verbrugh HA , Touw DJ . Colistin: Revival of an Old Polymyxin Antibiotic. 2015 Aug;37(4):419-27.

[16] Dhariwal AK , Tullu MS . Colistin: re-emergence of the 'forgotten' antimicrobial agent. 2013 Jul-Sep;59(3):208-15 Lupo A , Haenni M , Madec JY . Antimicrobial Resistance in Acinetobacter spp. and Pseudomonas spp. 2018 Jun;6(3).

[17] Berthelot P, Grattard F, Mahul P, et al. Prospective study of nosocomial colonization and infection due to Pseudomonas aeruginosa in mechanically ventilated patients. Intensive Care Med. 2001;27(3):503–512.

[18] Joseph L. Kuti,Aryun Kim, Daniel J. Cloutier &David P. Nicolau .Evaluation of Plazomicin, Tigecycline, and Meropenem Pharmacodynamic Exposure against Carbapenem-Resistant Enterobacteriaceae in Patients with Bloodstream Infection or Hospital-Acquired/Ventilator-Associated Pneumonia from the CARE Study (ACHN-490-007) .Infectious Diseases and Therapy volume 8, pages383–396(2019).

[19] C.-A.LiangY.-C.LinP.-L.LuH.-C.ChenH.-L.ChangC.-C.Sheu Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant Acinetobacter baumannii . Clinical Microbiology and Infection .Volume 24, Issue 8, August 2018, Pages 908.e1-908.e7.

[20] Gennaro De Pascale,Luca Montini, Mariano Alberto Pennisi,Valentina Bernini, Riccardo Maviglia,Giuseppe Bello, Teresa Spanu, Mario Tumbarello & Massimo Antonelli. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. Critical Care volume 18, Article number: R90 (2014).

Sahar .I. Al-Niemat; Ph, "Moh'd Nour" Mahmoud Bani Younes; Ph, Jaafar Abd Alrahman Abu Abeeleh; Ph, and Amani Daoud Alshawabkeh; PharmD, "Synergistic Activity Comparison between Colistin/Tigecycline and Colistin/High Dose Meropenem against Carbapenem Resistant Enetrobacteriaceae in Critically Ill Patients with Ventilator Associated Pneumoniae," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 3, Issue 3, pp. 28-32, 2020.