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The Clinical Advantages of High Dose Meropenem/Tigecycline Combination versus Tigecycline Monotherapy against Carbapenem Resistant Enetrobacteriaceae in Septic Critically Ill Patients Who are Not Candidate to Colistimethate Sodium

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Abstract*— *Background: *Carbapenem-Resistant Enterobacteriaceae (CRE) prevalence is globally increased with the widely carbapenems used in clinical practices. The aim of this study is to evaluate the clinical usefulness of adding high dose extended infusion meropenem (2 g over 3 hours TID) to the standard dose of tigecycline (100 mg LD, 50 mg BID) in comparison to standard dose tigecycline monotherapy in CRE infected-colistin non-candidate critically ill patients.* ***Methods:*** *An observational review study was directed in our foundation which included 110 patients admitted to our adult ICU. All eligible patients' basic and tested data were recorded retrospectively through our institutional electronic medical records (Hakeem). All patient's continuous variables will be expressed as Mean±SD by using the independent and One Sample T-Test, respectively. Regarding categorical variables, Chi Square test will be used to express them as numbers with percentages.* ***Results:*** *Our eligible sample had a mean overall age of 56.1±8.75 years. 59 subjects (53.64%) were male and 51 subjects (46.36%) were female. The ICU and overall hospital stay days were significantly lower in Group I than in Group II with Mean±SD of 8.66±0.48 days and 10.3±0.58 days vs 21.6±0.50 days and 25.0±0.00 days, respectively. Regarding mortalities, the early, late, and overall 28-day ICU mortality were also significantly lower in Group I than in Group II with Number (%) of 3 (5.36%), 8 (14.29%), and 11 (19.64%) vs 14 (25.93%), 24 (44.44%), and 38 (70.37%), respectively.* ***Conclusion:*** *In conclusion, our study shows that high dose extended meropenem infusion may mitigate the PK/PD barriers of tigecycline in treating septic critically ill patients and increases our available options in case of non-candidacy to colistin treatment and shortage of newer anti-CRE ABs.*

***Keywords*—** *Carbapenem Resistant Enterobacteriaceae, Colistimethate sodium, Critically ill patients, High dose extended infusion meropenem, Mortality, Tigecycline.*

I. INTRODUCTION

Carbapenem-Resistant Enterobacteriaceae (CRE) prevalence is globally increased with the widely carbapenems used in clinical practices. The increasing prevalence of multi-drug resistant gram negative bacteria (MDR-GNB), including CRE, is associated with overall hospitalized and critically ill patients morbidities and mortalities. Enterobacteriaceae are common pathogens causing a variety of severe infections, including community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (CIAIs), and bloodstream infections (BSIs). Enterobacteriaceae associated BSI is one of the most common types of infection associated with CRE. [1-3] Enterobacteriaceae associated carbapenem resistant is commonly emerged after frequently carbapenems administration for extended spectrum β-lactamase (ESBL) and AmpC cephalosporinase (AmpC) GNB. Carbapenems which are the most expanded and least B-lactamases susceptible β-lactam antibiotics, may gain resistant via carbapenemase with or without other non-β-lactamase mechanisms. Carbapenemase producing enterobacteriaceae (CPE), subtype of CRE family, is uniquely characterized by extensive carbapenemase production as the sole mechanism of resistant and an elevated carbapenem's MIC. [4-7]

Carbapenemase have the ability to hydrolyze all the known cephalosporins, monobactams, and carbapenems. In contrast to non-β-lactam β-lactamase inhibitors (NBLBLIs), all β-lactam β-lactamase inhibitors (BLBLIs) are poor substrate to carbapenemase, thereby leading to fewer numbers of effective anti-CRE antibiotics. CRE treatment options are limited, and these usually involve the use of colistin, tigecycline (TGC),

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fosfomycin, plazomicin, and the newer generation of β-lactam/NBLBLIs of ceftazidime/avibactam, meropenem/vaborbactam, Imipenem/relebactam, aztreonam/avibactam as the mainstays of therapy. Colistimethate sodium (Colistin®), prodrug of polymyxin E, is commonly used in our institution as a salvage option in cases of difficult to treat CRE infections. Colistin is commonly associated with nephrotoxicity especially in critically ill patients which reprioritize tigecycline as the drug of choice in some case scenarios. [8-11]

The primary barrier of tigecycline administration is its pharmacokinetics /pharmacodynamics drawbacks especially in critically ill patients. Pharmacologically, TGC is a glycylcycline antibiotic with a broad spectrum antibacterial activity. TGC has been used as a salvage treatment option against MDR-gram positive and negative bacteria. However, the efficacy of the standard dose of TGC in bloodstream infections (BSI) is still a matter of controversy mainly because of the low serum concentrations that can be achieved with TGC. Doubling the dosage of TGC may be a reasonable clinical strategy, but few studies have evaluated its effectiveness and safety when dealing with CRE associated BSI. High-dose, prolonged/extended infusion carbapenems can achieve a reliable bactericidal effects in GNB's MIC up to 16 mcg/ml. [12-13]

The aim of this study is to evaluate the clinical usefulness of adding high dose extended infusion meropenem (2 g over 3 hours TID) to the standard dose of tigecycline (100 mg LD, 50 mg BID) in comparison to standard dose tigecycline monotherapy in CRE infected-colistin non-candidate 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

An observational review study was directed in our foundation of King Hussein Medical Hospital (KHMH) in critically care unit at Royal Medical Services (RMS) in Jordan between April 2017 to April 2019. This study was endorsed by our Institutional Review Board (IRB), and a necessity for consent was deferred attributable to its retrospective plan. This investigation included 110 basically sick patients admitted to our adult ICU by means of the emergency department (ED) or through other hospital wards with any clinical or surgical issues. Absolutely, 996 ICU patients were rejected in light of the fact that they either released, had carbapenem affectability, or died before finished at least 1 week after ICU admission (676 members) or on the grounds that the necessary information couldn't be enlisted (320 members).

Patients' demographics, diagnostics, anthropometrics, hemodynamic parameters, empirical ABs for first 3 days of ICU admission, directed ABs that were used after culture results, microbiological results, clinical and laboratory responses, 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). In our study, non-candidacy to colistin therapy included critically ill patients with an uptrending status in acute kidney injury (AKI) and muscle weakness, already utilizing colistin treatment 2 full courses of 14 days and more, and had documented colistin hypersensitivity. All patient's continuous variables will be expressed as Mean±SD by using the independent and One Sample 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 110 septic mechanically ventilated critically ill patients admitted to our adult ICU with mean overall age of 56.1±8.75 years. 59 subjects (53.64%) were male and 51 subjects (46.36%) were female. The 28-day survival was significantly higher in antibiotic regimens that included tigecycline in combination with high dose extended infusion meropenem group (Group I) compared with tigecycline standard dose monotherapy (Group II) with Number (%) of 45 (80.36%) versus 16 (29.63%), respectively. The %Δ in white blood cells and theirs differential counts of neutrophils and monocytes ((%ΔWBCs, %ΔANC, and %ΔMC, respectively) were significantly lower in Group II compared with Group I with Mean±SD of -25.4%±4%, -31.7%±5%, and -43.4%±4% vs -12%±1.3%, -14.9%±2%, and -29.4%±1%, respectively. In contrast, the % Δ in ratios of neutrophils and monocytes to lymphocytes (%ΔNLR and %ΔMLR) were significantly higher in Group I compared with Group II with Mean±SD of -70.8%±15% and -75.7%±12% vs -32.9%±34% and -44.4%±28%, respectively. These % Δ in WBCs and theirs differentials were inversely trended with %ΔALB and MAP_{avg} and directly trended with %ΔCRP: ALB, NE_{avg}, and T_{avg}. Group I had significantly higher %ΔALB and MAP_{avg} in comparison with Group II with Mean±SD of 33.5%±17% and 79.9±1.22 mmHg vs 24.8%±12% and 71.1±1.95 mmHg. In contrast, Group II had significantly higher %ΔCRP:ALB, NE_{avg}, and T_{avg} than in Group I with Mean±SD of 395%±54%, 8.04±0.36 mcg/min, and 38.2±0.19 ° C vs 179%±30%, 6.54±0.17 mcg/min, 37.3±0.12 °C.

The ICU and overall hospital stay days were significantly lower in Group I than in Group II with Mean±SD of 8.66±0.48 days and 10.3±0.58 days vs 21.6±0.50 days and 25.0±0.00 days, respectively. Regarding mortalities, the early, late, and overall 28-day ICU mortality were also significantly lower in Group I than in Group II with Number (%) of 3 (5.36%), 8 (14.29%), and 11 (19.64%) vs 14 (25.93%), 24 (44.44%), and 38 (70.37%), respectively. Demographics, anthropometrics, research facility information, healthful information, microbiological and anti-infection data, complete blood checks and rates, clinical results of the investigation's basically critically ill patients among the two investigated groups are completely condensed in Table 1-3.

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

Variables		Total (N=110)	Group I (N=56)	Group II (N=54)	P-Value
Age (Yrs)		56.1±8.75	55.8±8.45	56.5±9.25	0.01 (S)
Sex	F	51 (46.36%)	28 (50%)	23 (42.59%)	0.106 (NS)
	M	59 (53.64%)	28 (50%)	31 (57.41%)	
BW (Kg)		75.1±10.6	76.5±11.7	73.7±9.44	0.07(NS)
BMI (Kg/m^2)		26.7±4.31	26.8±4.34	26.6±4.27	0.11 (NS)
CRP_1 (mg/dl)		40.5±16.9	34.5±15.9	46.5±17.9	0.00 (S)
ALB_1 (g/dl)		2.71±0.27	2.64±0.25	2.78±0.31	0.00 (S)
$CRP:ALB_1$		12.5±6.01	10.5±5.34	14.4±6.68	0.00 (S)
CRP_{avg} (mg/dl)		8.33±3.21	9.06±3.38	7.59±3.03	0.00 (S)
ALB_{avg} (g/dl)		3.38±0.34	3.36±0.31	3.39±0.38	0.00 (S)
%ΔALB		29.5%±15%	33.5%±17%	24.8%±12%	0.00 (S)
CRP: ALB_{avg} (X: 1)		3.23±1.58	3.58±1.69	2.88±1.44	0.00 (S)
%ΔCRP:ALB		281%±44%	179%±30%	395%±54%	0.00 (S)
$H.ALB_{avg}$ (g/day)		7.01±5.33	7.50±5.04	6.52±5.66	0.00 (S)
T_1 (°C)		38.1±0.15	37.8±0.12	38.7±0.19	0.00 (S)
T_{avg} (°C)		37.73±0.14	37.3±0.12	38.2±0.19	0.00 (S)
SBP_{avg} (mmHg)		106±1.52	110±1.22	101±1.95	0.00 (S)
DBP_{avg} (mmHg)		60.9±1.55	64.9±1.22	56.1±1.95	0.00 (S)
MAP_{avg} (mmHg)		75.8±1.49	79.9±1.22	71.1±1.95	0.00 (S)
HR_{avg} (bpm)		99.8±1.68	95.0±1.22	104±1.95	0.00 (S)
NE_{avg} (µg/min)		7.29±0.22	6.54±0.17	8.04±0.36	0.00(S)
TC_{avg} (Cal/day)		1388±235	1358±233	1402±238	0.06 (NS)
PD_{avg} (g/100 Cal)		3.75±0.74	3.78±0.76	3.70±0.71	0.15 (NS)
HC	Positive	57 (51.82%)	29 (51.79%)	28 (51.85%)	0.29 (NS)
	Negative	53 (48.18%)	27 (48.21%)	26 (48.15%)	
Day(s) Pre-ICU		2.51±0.49	1.66±0.48	3.43±0.50	0.00 (S)
ICU Stay $day_{(s)}$		11.8±5.5	8.66±0.48	21.6±0.50	0.00 (S)
Hospital Stay day(s)		14.6±0.32	10.3±0.58	25.0±0.00	0.00 (S)
28-day ICU Survival		61 (55.45%)	45 (80.36%)	16 (29.63%)	0.00 (S)
28-day ICU MOR		49 (44.55%)	11 (19.64%)	38 (70.37%)	
Early MOR (≤14 d)		17 (15.45%)	3 (5.36%)	14 (25.93%)	
Late MOR (>14 d)		32 (29.09%)	8 (14.29%)	24 (44.44%)	

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

Group I: Critically ill patients on Tigecycline+Meropenem.
Group II: Critically ill patients on Tigecycline monotherapy.
1: Baseline after ICU admission.
2: After 1 week of ICU admission.
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.
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	Total (N=110)	Group I (N=56)	Group II (N=54)	P-Value
$WBCs_1$ (×10^{3}Cells/µl)	18.5±1.89	16.4±2.09	21.1±1.69	0.00(S)
ANC_1 (×10^{3}Cells/µl)	15.3±2.01	12.9±2.11	18.3±2.11	0.00 (S)
$\%Neut_1$	81.5%±4.7%	78.3%±5.2%	86.8%±4.1%	0.00(S)
MC_1 (×10^3 Cells/µl)	2.01±0.29	1.66±0.27	2.35±0.27	0.00 (S)
$\%M_1$	10.45%±0.8%	10.0%±0.7%	11.1%±0.5%	0.00 (S)
TLC_1 (×10^3 Cells/µl)	1.09±0.87	1.17±0.76	1.01±0.71	0.00(S)
$\%LYM_1$	6.3%±4.4%	7.3%±4.9%	4.9%±3.6%	0.03 (S)
NLR_1 (X:1)	53.5±32.2	24.1±33.8	94.4±31.0	0.02 (S)
MLR_1 (X:1)	7.30±19.8	3.08±4.33	12.1±39.8	0.02 (S)
$WBCs_2$ (×10^3 Cells/µl)	15.04±1.91	12.3±2.03	18.5±1.65	0.00 (S)
ANC_2 (×10^3 Cells/µl)	11.7±1.91	8.87±1.85	15.6±1.94	0.00(S)
$\%Neut_2$	77.1%±4.6%	71.6%±5.0%	83.9%±4.0%	0.00(S)
MC_2 (×10^3 Cells/µl)	1.23±0.48	0.94±0.19	1.66±0.21	0.00 (S)
$\%M_2$	8.3%±0.7%	7.6%±0.5%	8.9%±0.4%	0.00 (S)
TLC_2 (×10^3 Cells/µl)	1.89±0.71	2.49±0.59	1.28±0.69	0.00 (S)
$\%Lym_2$	14.7%±6.3%	20.8%±5.6%	7.2%±4.5%	0.00 (S)

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NLR_2 (X:1)	10.16±8.22	3.78±1.31	16.5±10.7	0.00 (S)
MLR_2 (X:1)	0.97±1.11	0.40±0.14	1.75±1.14	0.00 (S)
%ΔWBCs	-18.9%±2.9%	-25.4%±4%	-12%±1.3%	0.00 (S)
%ΔANC	-23.6%±4%	-31.7%±5%	-14.9%±2%	0.00 (S)
%ΔMC	-36.9%±3%	-43.4%±4%	-29.4%±1%	0.00 (S)
%ΔTLC	269%±226%	263%±383%	279%±108%	0.00 (S)
%ΔNLR	-54.5%±30%	-70.8%±15%	-32.9%±34%	0.00 (S)
%ΔMLR	-60.1%±19%	-75.7%±12%	-44.4%±28%	0.00 (S)

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

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

Variables		Total (N=110)	Group I (N=56)	Group II (N=54)	P-Value
EMP ABs 1st 3-4 days	CFP	28 (25.45%)	16 (28.57%)	12 (22.22%)	0.110 (NS)
	PIP/TAZ	30 (27.27%)	14 (25.00%)	16 (29.63%)	
	MER	26 (23.64%)	12 (21.43%)	14 (25.93%)	
	IMP/CIL	26 (23.64%)	14 (25.00%)	12 (22.22%)	
CrCl (ml/min)		33.5±14.21	45.9±21.3	21.9±4.12	0.00 (S)
Meropenem (mg/day)		4375±934	4375±934	0.00±0.00	0.00(S)
MDR-GNB	CRE-E.Coli	28 (25.45%)	14 (25.00%)	14 (25.93%)	0.00(S)
	CRE-K.P	18 (16.36%)	8 (14.29%)	10 (18.52%)	
	CRE-E.spp	18 (16.36%)	10 (17.86%)	8 (14.81%)	
	CRE-S.M	11 (10.00%)	4 (7.14%)	7 (12.96%)	
	CRE-P.spp	15 (13.64%)	8 (14.29%)	7 (12.96%)	
	CRE-C.spp	20 (18.18%)	12 (21.43%)	8 (14.81%)	

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

Group I: Critically ill patients on Tigecycline+Meropenem.
Group II: Critically ill patients on Tigecycline 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.
EMP: Empirical antibiotics.
CRE: Carbapenem-resistant *Enterobacteriaceae.*
E.Coli: Escherichia.Coli.
K.P: Klebsiella. Pneumonia.
E.spp: Enterobacter.Species.
S.M: Serratia.Marcescens.
P.spp: Providencia.species.
C.spp: Citrobacter.species.
CEP: Cefepime.
PIP/TAZ: Piperacillin/Tazobactam.
MER: Meropenem.
IMP/CIL: Imipenem/Cilastatin.

IV. DISCUSSION

Only a few studies investigate the possibility of bypassing pharmacokinetic/pharmacodynamic barriers of the widely distributed, bacteriostatic tigecycline compared the clinical outcomes and effectiveness between tigecycline combination and monotherapy in critically ill patients. But what is unique in our study is that we compared the dual-antibiotic regimens that included standard dose regimen of tigecycline in combination with high dose extended infusion meropenem versus the mono-antibiotic regimen with standard dose tigecycline in septic critically ill patients. This dose regimen strategy is based on two theoretical principles in infectious disease of sepsis. Tigecycline has a PK/PD limitations that block its preferred position of high powerlessness rate in treating septic critically ill patients (Principle 1), and carbapenems including meropenem might be successful in vivo however it is resistant in vitro as long as the MIC of meropenem not surpasses 16 mcg/ml when utilized most extreme portion of 2 g TID and implanted over in any event 3 hours for each portion in plan to accomplish at least 100% fT> MIC (Principle 2). [14-16]

The tigecycline dose used in this study is the standard dose of 100 mg loading dose followed by 50 mg twice daily and the mean meropenem renal adjusted doses used in our study was 5778±634 mg/day in which the total daily dose of meropenem was divided into three doses each infused over 3 hours. Also, 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 tigecycline, and meropenem extended infusion (over 3 hours) which were also insignificant. The CRE family of Enterobacter.Species, Serratia.Marcescens, Providencia.species, Citrobacter.species, Escherichia.Coli, and Klebsiella. Pneumonia were significantly distributed among the two tested groups. Objective measures of hemodynamic parameters, vasopressor rates, and the interesting ratios of CRP and ALB, were

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assessed in our study in addition to WBC differential ratios to evaluate the outcome impacts among the studied groups as signs of systemic inflammatory response syndrome (SIRS) secondary to sepsis were improved as antibiotic regimens were considered more successful. As the ALB escaping rate from intravascular compartment into the interstitial compartment is highly dependent on the capillary vasodialtory status which is subsequently related to the GNB exotoxin and CRP levels, we took into consideration the clinical impacts of CRP:ALB ratio, nutritional status, and corticosteroids on the assessed outcomes of our study. In our study, the total calorie (TC) inputs, protein density inputs, and hydrocortisone replacement doses of 200 mg/day (commonly used in refractory septic shock patients) were insignificantly different among the two groups, which precluded their exaggerated confounding effects on NLR and MLR.

V. CONCLUSION

In conclusion, our study shows that high dose extended meropenem infusion may mitigate the PK/PD barriers of tigecycline in treating septic critically ill patients and increases our available options in case of non-candidacy to colistin treatment and shortage of newer anti-CRE ABs. 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.

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