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A Prospective Study Comparing Colistin-Tigecycline and Colistin-Meropenem Combination Therapies for Multidrug-Resistant *Klebsiella pneumoniae* Bloodstream Infections

Salma W Abdalla [1], Hoda A Salem [2], Maged S Abdalla [3], Zeinab A Zalat [2]

[1]Department of Clinical Pharmacy, Kasr Alainy Hospital, Cairo, Egypt.
[2]Department of Clinical Pharmacy, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo, Egypt.
[3]Department of Anesthesia and Intensive Care, Kasr Alainy Hospital, Faculty of Medicine, Cairo University, Giza, Egypt.

* Correspondence: e-mail@e-mail.com; Tel.: salma9793@gmail.com.

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Abstract: This study examined the effectiveness and safety profile of different combination therapies involving colistin in patients with multidrug-resistant Klebsiella pneumoniae (MDR-KP) bloodstream infections. Despite colistin's known toxicity, it was used in conjunction with other antibiotics to enhance its antibacterial impact. Specifically, the research compared two treatment regimens: one group received a colistin intravenous (IV)9 million International Units (mIU) loading dose, followed by a maintenance dose of 4.5 mIU every 12 hours (q12h), paired with tigecycline as a 100 mg loading dose infusion over 1 hour followed by a 50 mg maintenance dose infusion over 1-hour q12h; the second group received the same colistin dosing but combined with meropenem, administered as 2.0 g IV over 30 minutes q8h. The primary endpoint was in-hospital mortality, while secondary outcomes included evaluating the adverse effects of the treatments, such as nephrotoxicity, neurotoxicity, hepatotoxicity and hematological changes. Sixty patients participated, divided evenly between the two treatment groups. Over a 14-day treatment period, the group treated with colistin-tigecycline showed a marked reduction in mortality (66.67%) compared to the colistin-meropenem group [(4/30) vs. (12/30) p=0.0391]. The colistin-tigecycline regimen did not lead to significant adverse effects, and surviving patients demonstrated a reduction in procalcitonin levels, along with improved Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores. Notably, 8 patients exhibited elevated C-reactive protein (CRP) levels (p=0.0055). These findings highlight that colistin paired with tigecycline is more effective and safer than colistin with meropenem for treating MDR K. pneumoniae -induced bloodstream infections.

Keywords: Multidrug-resistant, Klebsiella pneumoniae, blood stream infection, combination therapy, tigecycline, colistin, meropenem.

1. INTRODUCTION

Carbapenem-resistant Klebsiella *pneumoniae* (CR-KP) is a threatening remark both for patients as well as healthcare systems, globally. The fact that infections due to MDR-KP strains are resistant to three or more antimicrobial agents, is not just adding a concern to critically ill patients but are also associated with high morbidity and mortality rates, prolongation of hospitalization and absolutely more costs[1-2]. Unfortunately, treatment choices are limited including aminoglycosides, colistin, tigecycline and fosfomycin[3-4,11].

Moreover, the incline in those antibiotics' usage has been followed by reports about the inception of Gram-negative isolates resistance to these medications[2,8]. The medical society has been stimulated to reconsider last lines of antibiotics as colistin and tigecycline, due to Gram negative bacteria role in developing resistance to most available antibiotics[1,2]. The polymyxin family is a polypeptide antibiotic including five different

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chemical compounds, specifically polymyxin A to E. The mechanism of action of colistin (polymyxin E) leading to cell death through a disruptive physiochemical impact followed by an alteration in cell membrane permeability[5]. Through early decades from 60th till 90^{th,} the colistin use was limited due to the rising occurrence of life-threatening toxicities, particularly nephrotoxicity[5-6]. However, the reintroduction of colistin use was initiated recently owing to its considerable advantage towards most Gram-negative bacteria, including MDR bacteria[7].

Tigecycline, a glycylcycline antibiotic authorized by the Food and Drug Administration (FDA) for treating complex intra-abdominal infections and skin structure infections in adults, has been established to be effective against *Enterobacteriaceae* and Klebsiella *Pneumoniae* even if carbapenemase producer. Its mechanism of action is mainly by inhibiting the bacterial protein synthesis and it was found to be bacteriostatic. Susceptibility testing data indicates that CR-KP infections commonly requires the usage of tigecycline or colistin as final medical options; meropenem in many cases also maintain phenotypic activity against Klebsiella *pneumoniae* Carbapenemase (KPC)-producers and is considered as a potential choice[14].

Nevertheless, raised colistin minimum inhibitory concentrations (MICs) have been declared with a raise in resistible strains of K. *Pneumoniae* infections due to these pan-resistant strains clear out most of the therapeutic choices. In case there is a need for beneficial treatment options, combinations of two or more antibiotics are usually sought for attaining synergistic effects[9-11]. Recent research has been performed showed that tigecycline along with colistin at relevant dosage intervals was approved to be an acceptable therapeutic option for infectious diseases caused by MDR KPC-producers especially when bactericidal outcome is required in cases as in bacteremia, endocarditis or other severe infections.

Based on the data presented, this research represents the first prospective investigation to assess and compare the efficacy and safety of colistin-tigecycline versus colistin-meropenem combination therapies in treating bloodstream infections (BSI) induced by MDR K. *pneumoniae*.

2. METHODS

2.1. Study design

This is a study that was applied on sixty adult patients (age group ≥ 20 years) suffering from bloodstream infections induced by MDR K. *pneumoniae*, was a prospective, single-blind, randomized through computerized database, comparative trial. Patients were randomly assigned to one of two treatment groups (n = 30 per group):

Group 1(n=30) received Intravenous (IV) colistin 9 mIU (million International Unit) IV infusion over 2 hours loading dose followed by maintenance dose 4.5 mIU IV infusion over 2 hours every 12 hours (q 12 h) plus IV tigecycline 100 mg IV infusion over 1 hour loading dose followed by maintenance dose 50 mg IV infusion over 1 hour q 12 h.

Group 2 (n = 30) received IV colistin 9 mIU IV infusion over 2 hours loading dose followed by maintenance dose 4.5 mIU IV infusion over 2 hours q 12 h plus IV meropenem 2.0 g IV infusion over 30 minutes every 8 hours (q 8 h).

The study was conducted between September 2019 and November 2020 at the General ICU of Qasr El-Aini Hospital, Cairo University. Ethical approval was obtained from the Cairo University hospital's Ethics Committee prior to study initiation.

2.2. Inclusion criteria

Patients were eligible if they had a confirmed bloodstream infection with CR-KP based on positive blood culture within the previous 5 days and met the diagnostic criteria outlined by the Infectious Diseases Society of America (IDSA)[16]. All patients were critically ill and hospitalized in the ICU.

2.3. Exclusion criteria

Exclusion criteria encompassed any patient without a confirmed multidrug-resistant Carbapenem-resistant K. *pneumoniae*-positive blood culture. Patients were also excluded if they had a Glasgow Coma Scale (GCS) score of less than 9 (for non-ventilated patients) or less than 6 (for ventilated patients), had metastatic malignant end stage cancer, or were terminal with APACHE II or SOFA scores exceeding 34 or 15, respectively. Patients with a mortality risk greater than 85% or 80% on the first day of colistin treatment, as assessed by APACHE II or SOFA scores, were also excluded[17-18]. Any patient who received IV colistin combination therapy for less than 72 hours was not included for additional analysis. Moreover, any patient with allergies to any of the administered medications (colistin, tigecycline and meropenem) was excluded from the study.

2.4. Microbiological testing

Blood cultures were collected from all participants at day 0 and 48 hours after treatment completion. Standard microbiological methods were applied for antimicrobial susceptibility testing as well as to identify causative organisms. Meropenem susceptibility was assessed by disk diffusion while

the broth microdilution technique was used to determine the susceptibility of colistin and tigecycline based on the guidelines of Clinical and Laboratory Standards Institute (CLSI)[19-21].

2.5. Colistin administration

Colistin (Colomycin; Forest Laboratories, UK Limited, Bexley, Kent, United Kingdom) was administered as a 9 mIU loading dose ahead of a 4.5 mIU maintenance dose every 12 hours. Dosage was adjusted based on kidney function (Creatinine clearance; CrCl) and renal replacement therapy protocols[22] **(Table I).**

2.6. Meropenem dosage administration

Fifty percent of the study participants were treated with meropenem (Meronem, AstraZeneca, United Kingdom) as part of a combined therapy aimed at managing severe infections caused by MDR Gram-negative bacteria. Patients with normal renal function received a dosage of 2000 mg q 8 h. Abnormal kidney function below 51ml/min requires dose adjustment as shown in the table below. There is limited information to support the intake of these dose adjustments for a unit dose of 2000 mg **(Table II).** Meropenem is cleared from the body by hemodialysis and hemofiltration, therefore, the required dose would be given post the hemodialysis cycle. For patients undergoing peritoneal dialysis, there are no established dose recommendations[23, 24].

2.7. Tigecycline dosage administration

The other half of patients received IV tigecycline (Tygacil, Pfizer) as a combined management for MDR Gram-negative bacterial infection as a single loading IV dose of 100 mg ahead of maintenance dose 50 mg IV q 12 h. Dose adjustment is not required for renal impaired patients or patients undergoing Regular Hemo-Dialysis (RHD). For impaired liver patients, dose adjustment is required for serious hepatic impairment (Child Pugh C) where 100 mg is given as single loading dose ahead of lowered maintenance dose of 25 mg q 12 h; no dose adjustment is required for patients with mild- moderate hepatic impairment (Child Pugh A & Child Pugh B)[25-26].

2.8. Outcomes

Primary Outcome: In-hospital mortality.

Secondary Outcomes: Adverse effects associated with the medications, including nephrotoxicity (assessed by serum creatinine (SCr), hepatotoxicity (evaluated by liver enzyme levels), neurotoxicity, and hematological changes (including thrombocytopenia).

Outcomes were interpreted as follows:

Cured: Patients were classified as cured if their infection symptoms and signs resolved by finishing the treatment protocol, accompanied by a reduction in SOFA and APACHE II scores for in-hospital mortality, and successful discharge from the ICU [27]. The decision to discontinue colistin-tigecycline or colistin- meropenem therapy was built on clinical status improvement, normalization of infection markers such as total leukocyte count (TLC), percentage of neutrophils, reduced C- reactive protein (CRP) as well as procalcitonin (PCT) levels below 0.5 ng/mL.

Improved: participants were considered improved if they showed partial improvements of infection symptoms and signs.

Unresponsive: participants were deemed unresponsive if their infection symptoms and/or signs persisted or worsened during the treatment.

Normal Renal Function is defined as a SCr level of ≤ 1.3 mg/dL, with the baseline starting SCr measured on first day of IV colistin administration. **Renal Function Deterioration** means worsening of renal function during colistin therapy was identified as an increase of more than 50% from start SCr level to a value >1.3 mg/dL or a deterioration in renal function necessitating renal replacement therapy.

2.9. Data collection

A detailed follow-up data collection sheet was used for collecting data required for this study specifically. Data were mainly SOFA and APACHE II scores on first and last day of medication administration[27-28,31], duration of medication administration, site(s) of infection, preceding antibiotic or antifungal use, concomitant antibiotic administration, mechanical ventilator support, presence of renal replacement therapy, duration of hospitalization.

Additionally, microbiological data including blood culture of the causative organism (Klebsiella *pneumonia*) at study day 0 and after 48 hours from end of treatment, additionally the in vitro susceptibility to different antimicrobial medications, including colistin, meropenem and tigecycline. Serum tigecycline level through 1st 24 hours (loading dose peak and trough level and 1st maintenance dose peak and trough level) as well as meropenem 1st dose peak and trough level were also collected and measured by Liquid Chromatography – Mass Spectroscopy (LC-MS). Moreover, biochemical tests such as renal/ liver function tests [SCr, Urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST)], CRP, haemoglobin, TLC, percentage of neutrophils and platelet count were collected and

Table 1. Colistin dosage adjustment based on kidney function.

Kidney function	Colistin maintenance dose administration
CrCl >60 ml/min	4.5 mIU q 12 h
CrCl ranging between 30–60 ml/min	3 mIU q 12 h
CrCl ranging between 10–30 ml/min	2 mIU q 12 h
CrCl <10 ml/min	1 mIU q 12 h
Intermittent hemodialysis	1mIU q12 h + supplemental dose of 1 mIU post each dialysis event
Continuous renal replacement therapy (CRRT)	4.5 mIU q12 h

Table 2. Meropenem dose adjustment

CrCl (ml/min)	Meropenem dose administration
CrCl of 26-50 ml/min	2000 mg q 12 h
CrCl of 10-25 ml/min	1000 mg q 12 h
CrCl <10 ml/min	1000 mg q 24 h

recorded daily during the treatment period. Furthermore, serum PCT value was measured at the end of treatment period as a biomarker to ensure dismissal of sepsis for patients with enhanced clinical condition as well as resolved signs and symptoms of infection together with regular values of TLC and percentage of neutrophils and serum CRP value improvement. The collected data in the patient collection sheets were handled through a computer database. In order to select candidates, there were numbered cards that were randomly selected. Moreover, infection type, causing microorganism and the clinical end result were decided by two blinded observers.

2.10. Sample size calculation

The PASS® version 11 program was used to determine the sample size, with a 95% confidence level and a 20.48% margin of error. Based on these values, a sample size of at least 26 individuals—raised up to 30 cases in each group—with bloodstream infection caused by MDR carbapenem-resistant K. *pneumoniae* were included in the study.

2.11. Statistical analysis

Qualitative data were represented as frequencies and percentages. Quantitative data were represented as mean plus standard deviation (SD) values. For qualitative data; Fisher's exact (FE) test was used for comparisons and Gehan-Breslow-Wilcoxon test (Chi square) for comparison of survival curves. Quantitative analysis of data was performed using Mann-Whitney (MW) test and Wilcoxon matched-pairs signed rank (WMP) test. The level of significance was set at $p \leq 0.05$. The statistical analysis was carried out using IBM Windows SPSS Statistics, Version 23.0. Armonk, New York: IBM Corp.

3. RESULTS

The study, conducted from September 2019 to November 2020, included 60 patients diagnosed with MDR-KP infections. Participants were treated with colistin plus tigecycline or colistin plus meropenem combination therapy. All data pertaining to these patients were collected, recorded, and reviewed by the ICU medical staff.

3.1. Patient characteristics

Table 3 outlines the demographic details (age, gender) as well as clinical profiles, including comorbidities, of the two patient groups treated with colistin + tigecycline (n = 30) or colistin + meropenem (n = 30). Major differences were not observed between the groups concerning demographics, infection type, or the contributing pathogen. Among the total cohort, 19 patients (31.7%) presented with abnormal baseline SCr levels (>1.3 mg/dL) on the 1st day of treatment.

Notably, col-tiga group had also showed significant decrease in duration of treatment till eradication of bacterial infection by 20.92% in comparison to col-mer group (p= 0.0001) with significant decrease in total length of ICU staying by 12.31% in comparison to col-mer group (p= 0.0063) **(Table 3).**

Table 3. Comparing patient groups at baseline among colistin + tigecycline and colistin + meropenem.

Demographics, clinical features and comorbidities of patients at baseline	**Colistin-tigecycline n = 30**	**Colistin–meropenem n = 30**	***p*-value**
Demographical data of assigned patients			
Gender (male)	22⁄30 (73.3%)	16⁄30 (53.3%)	0.1799
Age (years)	53.03 ± 13.42	50.23 ± 16.56	0.4294
APACHE II score	19.33 ± 5.791	19.40 ± 4.959	0.8801
SOFA score	10.97 ± 2.593	11.77 ± 2.359	0.2328
Patients with certain co-morbidities at baseline			
Malignancy	2⁄30 (6.67%)	5⁄30 (16.67%)	0.4238
Heart dysfunction	6⁄30 (20%)	12⁄30 (40%)	0.1581
Lung dysfunction	8⁄30 (26.67%)	14⁄30 (46.67%)	0.1799
Diabetes mellitus	9⁄30 (30%)	13⁄30 (43.3%)	1.0000
Urogenital disorder	2⁄30 (6.67%)	5⁄30 (16.67%)	0. 4238
Chronic renal failure	8⁄30 (26.67%)	11⁄30 (36.67%)	0. 5796
Serum creatinine baseline (≥1.3 mg dl^{-1})	8/30 (26.67%)	11/30 (36.67%)	0.5796
Thrombocytopenia (platelets ≤ 150,000 count/µl)	2/30 (6.67%)	3/30 (10.00%)	1.0000
Elevated aspartate aminotransferase (AST) (> 40 U/L) & alanine aminotransferase (ALT) (> 56 U/L)	5/30 (16.67%)	8/30 (26.67%)	0. 5321
Hepatic disease	3⁄30 (10%)	5⁄30 (16.67%)	0.7065
Hematological disorder	2⁄30 (6.67%)	6⁄30 (20%)	0. 2542
Neurological disorder	13⁄30 (43.3%)	6⁄30 (20%)	0. 0946
Patients with previous hospitalization (within the last 3 months)	19⁄30 (63.3%)	24⁄30 (80%)	0. 2516
Patients with previous antibiotic use (within the last 3 months)	21⁄30 (70%)	26⁄30 (86.67%)	0. 2092
Patients with previous surgery	3⁄30 (10%)	8⁄30 (26.67%)	0. 1806
Days of hospitalization before the first day of treatment	15.03 ± 5.834	13.53 ± 4.974	0. 3903
Days of intensive care unit (ICU) stay of survived patients	14.96 ± 2.821	17.06 ± 2.338	0. 0063*

Patients on mechanical ventilation support	18⁄30 (60%)	23⁄30 (76.67%)	0. 2668
Patients receiving special treatments at baseline			
Anti-tumor treatment	2⁄30 (6.67%)	5⁄30 (16.67%)	0. 4238
Steroid treatment	14/ 30 (46.67%)	12⁄30 (40%)	0. 7948
Blood transfusion	5⁄30 (16.67%)	3⁄30 (10%)	0. 7065
Hemodialysis	4⁄30 (13.3%)	2⁄30 (6.67%)	0. 6707
Urinary catheter	23⁄30 (76.67%)	26⁄30 (86.67%)	0.5062
Gastrostomy / colostomy	2⁄30 (6.67%)	3⁄30 (10%)	1.0000
Patients with certain site of infection that led to bacteremia			
Pneumonia	16⁄30 (53.3%)	23⁄30 (76.67%)	0.1033
Urinary tract infection	13⁄30 (43.33%)	8⁄30 (26.67%)	0. 2789
Abdominal infection	1⁄30 (3.33%)	3⁄30 (10%)	0. 6120
Surgical site infection	4⁄30 (13.3%)	1⁄30 (3.33%)	0. 3533
Skin and soft-tissue infection	2⁄30 (6.67%)	1⁄30 (3.33%)	1.0000
Central line-related infection	6⁄30 (20%)	4⁄30 (13.3%)	0. 7306
Bacteremia	30⁄30 (100%)	30⁄30 (100%)	1.0000
Pathogen isolated			
Klebsiella *pneumonia*e	30⁄30 (100%)	30⁄30 (100%)	1.0000
Antimicrobial susceptibility of the isolated pathogen			
MDR KPC- producers	21⁄30 (70%)	27⁄30 (90%)	0. 1042
MDR KPC- producers only susceptible to colistin	9⁄30 (30%)	3⁄30 (10%)	0. 1042

The data are expressed as mean ± SD and incidence percentages. Statistical analyses were conducted using the MW test and FE test to evaluate differences. Comparisons were made relative to the colistin-tigecycline combination therapy group (*).

Table 4. Comparing the mortality and survived rates among patients receiving colistin + tigecycline combination therapy *vs.* colistin + meropenem combination therapy.

Clinical outcomes	**Colistin-tigecycline n = 30**	**Colistin–meropenem n = 30**	***p*-value**
Mortality	4/30 (13.33%)	12/30 (40%)	0. 0391
Cured and survived	26/30 (86.67%)	18/30 (60%)	0. 0267

3.2. Mortality incidence and survival (as a primary goal)

By comparing 14-day mortality between critically ill patients with MDR Gram-negative Klebsiella pneumoniae infection as evaluation of the therapeutic activity of *colistin - tigecycline* vs.colistin - meropenem combined therapies, the following was observed; incidence of mortality by the end of the treatment, col-tiga group revealed significant decrease by 66.67 % in comparison to col-mer group (p = 0.0391). In addition, col-tiga group revealed significant increase in survival rate by 44.44 % at the end of the treatment in comparison to col-mer group (p = 0.0267) (Table 4, Fig. 1 A and B).

3.3. Clinical status evaluation

Regarding APACHE and SOFA scores, there was insignificant difference in APACHE and SOFA score start values of all patients of col-tiga group in comparison to col-mer group (*p*= 0.8801& 0.2328) respectively **(Table 3).** Regarding surviving patients, there were a significant decrease in APACHE score

by 75.69% in col-tiga group and 77.84% in col-mer group. While there was a significant decrease in SOFA score by 84.76% in col-tiga group and 81.82% in col-mer group by the end of treatment in comparison to start values in both col-tiga and col-mer groups, respectively (p= 0.0001) **(Table 5)**. Furthermore, there was no significant difference in APACHE and SOFA score end values of survived patients of col-tiga group in comparison to col-mer group (p=0.366 and 0.2728) respectively **(Table 6).**

3.4. Biochemical tests

Col-tiga and col-mer groups showed significant decrease in TLC value by 56.91 % & 57% at the end of the treatment in comparison to the TLC values at day 1 of the same group ($p < 0.0001$), respectively **(Table 5)**. On the other hand, Regarding TLC value by the end of the treatment, there was insignificant difference between the two groups. Moreover, col-tiga and col-mer groups showed significant decrease in neutrophils percentage by 25.4% & 29.21% at the end of the treatment in comparison to the % of neutrophils values at day 1 of the same group ($p < 0.0001$), respectively **(Table 5).** On the other hand, Regarding, % of neutrophils value by the end of the treatment, significant difference was not observed among the two groups.

Regarding starting value of CRP, significant difference was not observed among the two groups. On the other hand, both col-tiga and col-mer groups revealed significant decrease in CRP value by 82.17% & 79.33% ($p < 0.0001$) at the end of the treatment in in comparison to the starting value at day 1 of same group, respectively **(Table 5)**. However, regarding the CRP value at the end of the treatment, there was insignificant difference among the two treatment groups**.** Regarding procalcitonin level at the end of the treatment, there was insignificant difference among the two groups. Eight patients out of 44 survived patients in the two groups showed significant elevation in CRP level with normal procalcitonin by the end of the treatment which is statistically significant in comparison to 36 patients out of 44 that showed normal level of both parameters ($p = 0.0055$) **(Table 7).**

3.5. Comparing comorbidities (as secondary goal)

Comparing the comorbidities (nephrotoxicity, hepatotoxicity, neurotoxicity, hematological changes) between critically ill patients with MDR Gram-negative Klebsiella *pneumoniae* infection who were treated with colistin - tigecycline versus colistin - meropenem combined therapies

3.5.1. Nephrotoxicity

Regarding reversible kidney dysfunction incidence during treatment period, col-tiga group showed no significant difference in comparison to col-mer group (p= 0.771). For irreversible kidney dysfunction incidence, there was also insignificant difference among the two treatment groups (p= 0.6707) **(Table 8).** Moreover, regarding the time of occurrence of acute kidney injury (AKI), there was also insignificant difference among the two groups (p= 0.1953) **Fig 2. A and B.**

Col-tiga showed significant elevation in Cr levels to maximum levels during the treatments by 79.79% ($p < 0.0001$) in comparison to starting values at day 1. Although Cr levels at max levels were significantly decreased by 37.65% (p = 0.0553) at the end of treatment but were significantly increased by 18.17 % in comparison to day 1 values ($p < 0.0001$). Moreover, col-mer showed significant elevation in Cr levels to maximum levels during the treatments by 80.41% ($p < 0.0001$) in comparison to starting values at day 1. Cr levels at max levels were significantly decreased by 25.8% (p = 0.0231) at the end of treatment but were significantly increased by 33.90% in comparison to day 1 values (p= 0.0009) **(Figure 3. A, B, C, D).** Regarding urea levels in survived patients, there were no significant differences between starting values at day 1 and end values in both groups **(Table 5).**

3.5.2. Hepatotoxicity

Regarding elevated liver enzymes levels at day 1, the two groups revealed no significant difference **(Table 3)**, also, there was insignificant difference in number of incidences of liver enzymes elevation during treatment periods in both groups **(Table 9).** Moreover, there were no significant difference between the baseline day 1 levels of AST and ALT of col-mer group and the end of treatment values, col-tiga revealed no significant change in ALT values by the end of treatment in comparison to starting baseline day 1 values as well. Although, col-tiga revealed significant decrease by 8.5% at the end of treatment in AST values in comparison to starting baseline day values (p= 0.0146) **(Table 10).**

3.5.3. Hematological changes

Regarding the incidence of hemoglobin drop, there were insignificant difference between the two groups at day 1, during treatments or by the end of treatments. Moreover, there was insignificant difference in incidence of thrombocytopenia during treatments among the two groups (**Table 9**). Finally, there was an insignificant difference in platelets count between day 1 baseline values and at the end of treatments values among two groups (**Table 10**).

3.5.4. Neurotoxicity

There was insignificant difference among the two groups regarding incidence of neurological events in

Table 5. Comparing data from the 1st day of treatment (Start) to the final day of treatment (End) for treated patients with either colistin + tigecycline or colistin + meropenem combination therapy.

Colistin-tigecycline n = 26				
Parameters	**Start (value at the beginning of treatment)**	**End (value at the end of treatment)**	***p*-value**	**End – Start (start-treatment value subtracted from end-treatment value)**
Serum creatinine (SCr) (mg/dL)	0.9533 ± 0.3589	1.127 ± 0.4464	< 0.0001 *	0.1733 ± 0.2132
Urea (mg/dL)	33.96 ± 17.64	35.00 ± 20.23	0.8381	1.038 ± 5.118
Total leukocyte count (TLC) (count/µl)	19.91 ± 4.029	8.573 ± 0.8469	< 0.0001 *	-11.33 ± 3.835
Neutrophils % (count/µl)	86.62 ± 5.005	64.62 ± 7.049	< 0.0001 *	-22.00 ± 8.333
C-reactive protein (CRP) (mg/L)	177.8 ± 56.90	31.69 ± 37.07	< 0.0001 *	-146.1 ± 67.47
Procalcitonin (ng/mL)	-	0.1158 ± 0.04110	-	-
(SOFA) score	10.58 ± 2.533	1.654 ± 0.7971	< 0.0001 *	-8.923 ± 2.770
(APACHE) II score	18.35 ± 5.276	4.462 ± 2.420	< 0.0001 *	-13.88 ± 4.803
Colistin–Meropenem n = 18				
Parameters	**Start (value at the beginning of treatment)**	**End (value at the end of treatment)**	***p*-value**	**End – Start (start-treatment value subtracted from end-treatment value)**
Serum creatinine (SCr) (mg/dL)	0.9667 ± 0.3378	1.294 ± 0.9213	0. 0009 *	0.3278 ± 0.8982
Urea (mg/dL)	25.49 ± 17.06	30.17 ± 23.06	0.6380	4.672 ± 19.87
Total leukocyte count (TLC) (count/µl)	20.56 ± 4.679	8.839 ± 1.231	< 0.0001 *	-11.72 ± 4.500
Neutrophils % (count/µl)	87.50 ± 4.356	61.94 ± 4.263	< 0.0001 *	-25.56 ± 6.090
C-reactive protein (CRP) (mg/L)	150.5 ± 41.55	31.11 ± 38.54	< 0.0001 *	-119.4 ± 42.17
Procalcitonin (ng/mL)	-	0.1028 ± 0.0429	-	-
(SOFA) score	10.94 ± 2.413	1.944 ± 0.9376	< 0.0001 *	-9.000 ± 2.223
(APACHE) II score	16.56 ± 3.203	3.778 ± 2.290	< 0.0001 *	-12.78 ± 3.782

The data are represented as mean ± SD. The WMP test was used for statistical analysis, with a significance level of $p \leq 0.05$. (*) As compared to the colistin-tigecycline.

Table 6. Comparing SOFA and APACHE II scores on the final day of treatment for treated patients with either colistin + tigecycline or colistin + meropenem combination therapy.

Clinical outcome scores in survived patients	**Col-Tiga n= 26**	**Col-Mer n= 18**	***p*-value**
(APACHE) II end score	4.462 ± 2.42	3.778 ± 2.29	0.3666
(SOFA) end score	1.654 ± 0.7971	1.944 ± 0.9376	0.2728

The data are expressed as mean ± SD. Statistical analysis was performed using the WMP test, with significance set at $p \leq 0.05$.

Table 7. Comparing patient survival rates at the end of treatment, based on abnormal CRP and procalcitonin levels, between those receiving colistin + tigecycline versus colistin + meropenem combination therapy.

Laboratory parameters at the end of treatments	**CRP (>10mg/L)**	**Procalcitonin Levels (>2.0 ng/mL)**	***p*-value**
Survived patients (n= 44)	8/44 (18.18 %)	0/44 (0%)	0. 0055*

Data is presented as incidence percentages. FE test was used to perform statistical analysis.

Table 8. Renal dysfunction among patients receiving colistin + tigecycline combination therapy *vs.* colistin + meropenem combination therapy.

Clinical outcomes	Colistin-tigecycline n = 30	Colistin–meropenem n = 30	*p*-value
Reversible renal dysfunction	7/30 (23.33%)	3/30 (10%)	0. 2990
Irreversible renal dysfunction	2/30 (6.67%)	4/30 (13.33%)	0.6707
Hemodialysis	3⁄30 (10%)	2⁄30 (6.67%)	0.6120

Data is presented as incidence percentages. FE test was used to perform the statistical analysis.

Table 9. Comparing clinical morbidity outcomes among colistin + tigecycline and colistin + meropenem treated patients.

Clinical outcomes	Colistin-tigecycline n = 30	Colistin–meropenem n = 30	*p*-value
Patients with normal baseline level who showed liver enzymes elevation post therapy	5/30 (16.67%)	8/30 (26.67%)	0.5321
Patients with normal baseline showed thrombocytopenia post therapy	4⁄30 (13.33%)	7⁄30 (23.3%)	0.5062

Data is presented as incidence percentages. The statistical analysis method was FE test.

Table 10. Comparing laboratory data of survived patients treated among both treated groups between at the 1st day of treatment (Start) and the end of treatment (End)

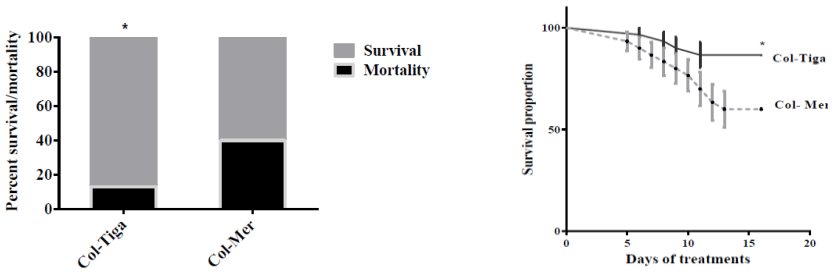
	Colistin-tigecycline n = 26			
Laboratory Parameters	**Start (value at the beginning of treatment)**	**End (value at end of treatment)**	***p*-value**	**End – Start (start-treatment value subtracted from end-treatment value)**
Platelets (count/µl)	294.1 ± 106.9*10^3	277.9 ± 106.1*10^3	0. 1306	-16.23 ± 46.67*10^3
Aspartate aminotransferase (AST) (U/L)	39.35 ±39.43	36.00 ±36.63	0. 0146	-3.346 ±6.368
Alanine aminotransferase (ALT) (U/L)	33.65 ± 34.03	35.15 ± 36.55	0. 1785	1.500 ± 5.457
	Colistin–meropenem n = 18			
Laboratory Parameters	**Start (value at the beginning of treatment)**	**End (value at end of treatment)**	***p*-value**	**End – Start (start-treatment value subtracted from end-treatment value)**
Platelets (count/µl)	304.3 ±113.4*10^3	268.6 ±110.7*10^3	0. 0616	-35.72 ± 69.40*10^3
Aspartate aminotransferase (AST) (U/L)	39.67 ±24.09	38.06 ±34.36	0. 0915	-1.611 ± 13.23
Alanine aminotransferase (ALT) (U/L)	36.72 ±25.35	33.72 ±32.16	0. 1778	-3.000 ±11.98

The data are represented as mean ± SD. Statistical analysis was carried out using WMP test. ($p \leq 0.05$).

form of seizures during treatments period **(Fig.4).**

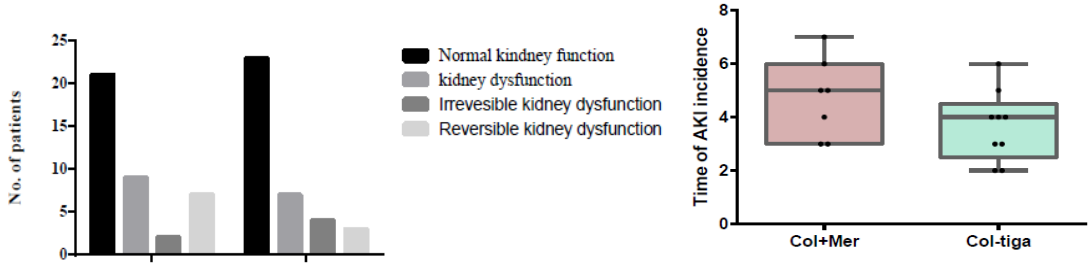
3.6. Pharmacokinetics evaluation of tigecycline peak serum concentration (C_{max}) and trough serum concentration (C_{min}) in Egyptian population

The peak concentration (Cmax) and minimum concentration (Cmin) and their times (Tmax and Tmin, respectively) were measured directly from serum concentration versus time. The mean peak and trough serum concentration versus time profiles of tigecycline following loading dose of 100 mg and first maintenance dose of 50 mg is shown in Figure 5. It was found that Cmax following loading dose administration (1.198 ±1.11) µg/ml was significantly higher compared to the maintenance dose (0.639 ± 0.02) µg/ml at ($p<0.0015$). In addition, it was found that Cmin following loading dose administration (0.14 ±0.03) µg/ml was significantly higher compared to the maintenance dose (0.11 ± 0.02) µg/ml at ($p<0.0004$).



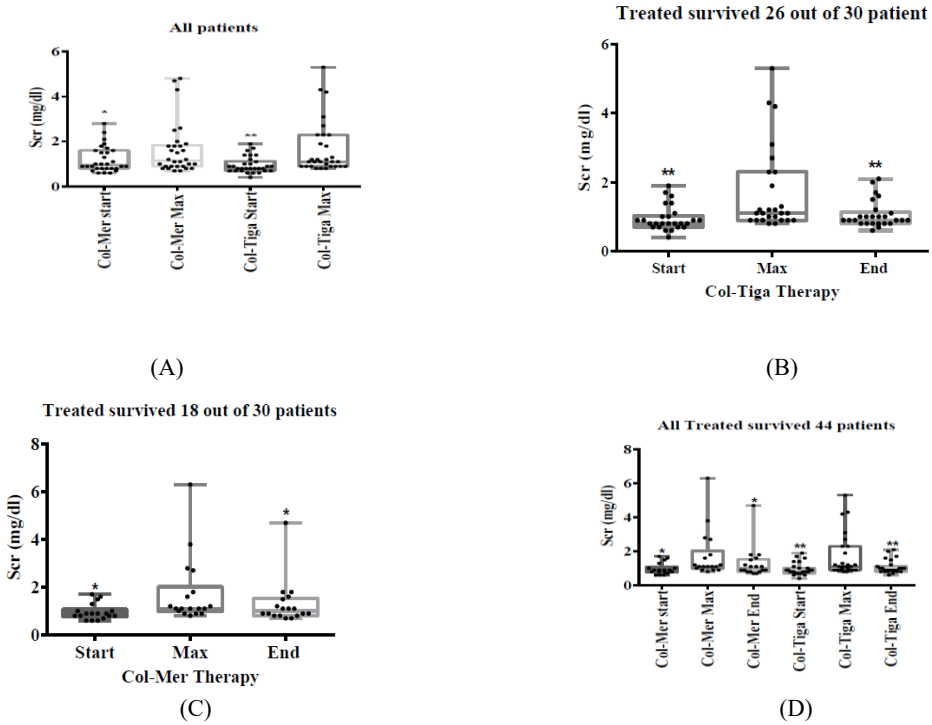
(A) (B)

Figure 1. Survival proportions were analyzed as follows: (A) Percentage of survival and mortality in the colistin + tigecycline (col-tiga) group compared to the colistin + meropenem (col-mer) group. (B) Percentage of survival in the col-tiga and col-mer groups. Statistical study was performed using the chi square test and FE test. A significance level of $p \leq 0.05$ was considered statistically significant when comparing outcomes to the col-mer group (*).



(A) (B)

Figure 2. (A) The distribution of candidates showing normal kidney function and those with renal dysfunction in the groups treated with col-tiga and col-mer. (B) The timing of AKI onset in patients receiving col-tiga or col-mer treatments. The mean and standard deviation of the number of days is represented by the horizontal lines within the boxes. Statistical evaluations were conducted using FE test and the MW test.



(A) (B)

(C) (D)

Figure 3. (A) all study patients, (B) col-tiga survived treated patients' group, (C) col-mer survived treated patients' group, (D) both treatments groups of all 44 survived patients, distribution of SCr levels on 1st day of treatment (Start), the peak value (Max) and the end of treatment (End) of SCr levels in col-tiga or col-mer therapy. Statistical analysis methods included WMP test. Significant difference ($p \leq 0.05$) from * col- mer (Max) and ** col–tiga (Max)

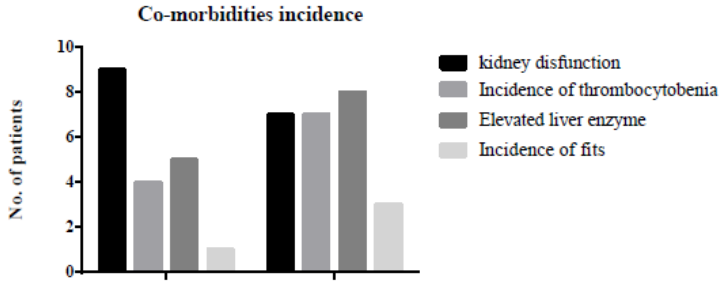


Figure 4. Co-morbidities incidence among col-tiga and col-mer groups. Statistical analysis methods included **FE test.**

3.7. Pharmacokinetics evaluation of meropenem peak serum concentration (C_{max}) and trough serum concentration (C_{min}) in Egyptian population

Regarding meropenem pharmacokinetics in the treated patients, the mean peak and trough serum concentration versus time profiles of tigecycline following dose of 2000 mg is shown in **Figure 6**. It was found that C_{max} following the first dose administration was (101.89 ± 9.58) µg/ml. In addition, it was found that C_{min} following the first dose administration was (0.53 ±0.04) µg/ml.

4. DISCUSSION

Since the world is currently facing a steep incline in abuse and/or misuse of antibiotics thus leading to severe antimicrobial resistance and leaving us with very limited options for treating infectious diseases caused by resistant strains of Gram-negative bacteria[28]. The choices are either the re-using of those overlooked antibiotics like colistin or the use of combination therapies. In this study, the two strategies were followed as the target of this study was to assess the role of colistin combined with meropenem versus role of colistin combined with tigecycline in curing 60 patients with bacteremia caused by MDR Klebsiella *pneumoniae*.

The outcomes of this study discovered that colistin – tigecycline combination therapy is superior to colistin-meropenem combination regarding patients' clinical improvement along with reduction in in-hospital mortality rates (as the primary goal for this study). In addition, regarding the occurrence of medications adverse effects such as nephrotoxicity, hepatotoxicity, neurotoxicity and hematological changes (as the secondary goal for the study), there was insignificant difference among the two groups. Supporting the current study, in vitro previous studies outlined that the colistin combined with tigecycline regimen showed superiority to other colistin combination therapies against Klebsiella *pneumoniae* and other Gram-negative microorganisms such as Pseudomonas *aeruginosa,* Acinetobacter *baumannii* as well as Escherichia *coli*[14-15]. Furthermore, T. Amat *et al*. showed in-significancy of colistin combination with tigecycline therapy, through a retrospective MDR A. *baumannii* bacteremia study. Opposing present study, T. Amat *et al.* study inclusion criteria included bacteremia induced by MDR Gram-negative bacteria Acinetobacter spp. not K. *Pneumoniae* with the similar loading colistin dose of 9 mIU but dissimilar maintenance dose of 9 mIU q24 h. Despite the aim of the formerly cited study and the present study, there were significant difference regarding the inclusion criteria and the design of the study applied by T. Amat *et al.* led to dissimilarities in the study results as well as conclusions[29].

Koch-Weser *et al*. had previously reported that colistin nephrotoxicity is considered one of the most important concerns while dealing with colistin[6]. Since 1990s, nephrotoxicity had become less adverse, perhaps due to the extra care, support treatment as well as supplementary fluid intake by the medical team on this potential toxicity. Conway and Falagas who were using 3-6 mIU dose of colistin, outlined that nephrotoxicity can be controlled; this had revived the use of colistin[30-31]. Eventually, the authors of another study revealed that 9 mIU of colistin did not cause nephrotoxicity events defending current study[32]. Furthermore, colistin plus meropenem did not reveal major permanent renal injury, that is in agreement with retrospective previous researches[33-34].

On the contrary, neurotoxicity is considered the least common adverse effect related to treatment with colistin as outlined by Koch-Weser *et al.*[6]. These researchers outlined a number of cases presenting signs of neurotoxicity as paresthesia, neuromuscular blockade or apnea in colistin-administered candidates. On the other hand, this was not the scenario here in our study neither in Falagas and Kasiakou study[31]. Moreover, there were no significant adverse events regarding liver enzymes elevation or thrombocytopenia with colistin combination therapies either with meropenem or tigecycline.

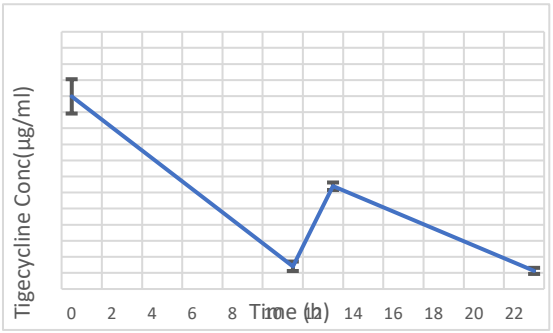


Figure 5. Tigecycline pk profile in Egyptian population and first maintenance dose of 50 mg (from time 12.5 to 23.5 hr).

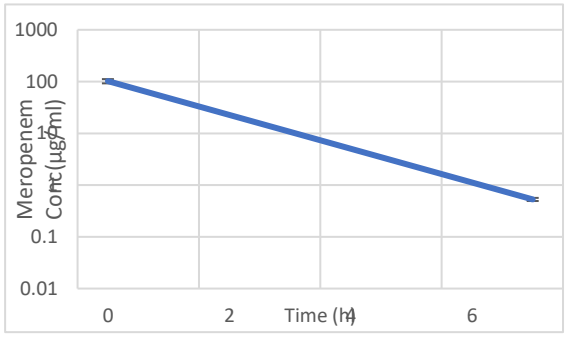


Figure 6. Meropenem pk profile in Egyptian population following first dose of 2 g.

The current study revealed that procalcitonin is significantly more specific than CRP in patients suffering from bacteremia. Kaziani *et al.* had also agreed on the fact that using PCT-based protocols does have a value in minimizing the period of antibiotic regimen administration for lowering antimicrobial resistance, enhancing clinical outcome as well as decreasing treatment costs[35]. Another study had reported the preferable advantage of using PCT as sepsis diagnostic biomarker as an alternative to the conventional laboratory parameters as raised TLC levels or CRP that are not able to differ between infectious and non-infectious inflammation[36], also PCT has shown supremacy in assorting whether its viral or bacterial infection compared to CRP[37]. Furthermore, either PCT alone or in combination with APACHE II or SOFA scores, PCT has revealed a remarkable practicality in determining sepsis occurrence in patients with suspected sepsis[38]. The present study in Egyptian population revealed the serum concentration pharmacokinetic (pk) pattern of first dose of meropenem 2 g in consistency with Khanh Q. Bui *et al.* study that was using the same administered dose[39]. Regarding tigecycline serum concentration pk profile of loading dose (100 mg) and first maintenance dose (50 mg), the present study revealed the same pk profile that revealed by Heather K. Sun *et al*. whom were examining the of the same administered dose[40].

5. CONCLUSIONS

In conclusion, this study demonstrates that colistin-tigecycline combination therapy is more effective and safer than colistin-meropenem for treating bloodstream infections caused by MDR Klebsiella *pneumoniae*. The significant reduction in in-hospital mortality, improved clinical outcomes, and manageable adverse effects support the use of colistin-tigecycline as a first-line treatment for these challenging infections. Future multicenter studies with larger sample sizes are needed to confirm these findings and further explore the optimal dosing and duration of combination therapies.

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Conflicts of Interest: All the authors assert that they have no potential conflicts of interest.

Ethical Statement: The research for this study was authorized by the Al-Azhar University, Faculty of Pharmacy (Girls) Ethical Committee and approved by the Cairo University, Kasr Alainy Hospital Research Ethics Committee (REC) with an approval code D1-2019. The study was also authorized by Clinical Trials. Gov with an ID (NCT04489459).

Author Contribution: Zeinab AlKasaby, Maged Salah Abdalla, and Salma Wagih Abdalla all confirmed their involvement in the article by contributing to plan and construct the study, as well as by doing formal analysis and analyzing the findings. Every stage of the investigation was directed by Zeinab AlKasaby. Hoda Salem and Maged Salah contributed to the research and design concept. Maged Salah assessed and interpreted the data. With the help of all authors, Salma Wagih carried out the experimental investigation, composed the article, executed the experiment, and produced the written paper. Finally, everyone agreed on the final draft of the manuscript.

List of Abbreviations: ALT: Alanine Aminotransferase, APACHE II: Acute Physiology and Chronic Health Evaluation II, AST: Aspartate aminotransferase, BSI: Blood-Stream Infection, CLSI: Clinical and laboratory standards institute,

$C_{max.}$: Maximum serum concentration, C_{min}: Minimum serum concentration, CrCl: Creatinine clearance, CRKP: carbapenem-resistant Klebsiella *pneumoniae,* CRP: C-reactive protein, CRRT: continuous renal replacement therapy, FDA: Food and Drug Administration, GCS: Glasgow Coma Scale, ICU: Intensive care unit, IDSA: Infectious Diseases Society of America, IU: International unit, IV: Intravenous, KPC: Klebsiella *pneumoniae* carbapenemase, LC-MS: Liquid Chromatography – Mass Spectroscopy, MDR: Multi-drug resistant, MIC: Minimum inhibitory concentration, MIU: Million International Unit, mmHg: Millimeters of mercury, ng: Nano-gram, PCT: Procalcitonin, PK: Pharmacokinetics, Q8h: Every 8 hours, RHD: Regular Hemo Dialysis, SCr: Serum creatinine, SD: Standard Deviation, SOFA: Sequential Organ Failure Assessment.

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