**ORIGINAL PAPER**

Surg. Gastroenterol. Oncol. 2022 eCollection October DOI: 10.21614/sgo-eC-432

# Tigecycline versus Meropenem Adjunctive Antibiotics for Septic Critically ILL Patients with Ruptured Appendicitis

Mahmoud AL-Awaysheh*

Faculty of Medicine, Mu'tah University, Al Karak, Jordan

***Corresponding author:**
Mahmoud AL-Awaysheh, MD, MRCSI
consultant general and colorectal surgery
Faculty of Medicine
Mu'tah University, Al Karak, Jordan
E-mail: Dr.mahmoud60@yahoo.com

## ABSTRACT

**Objectives:** Recently, there are emerging evidence of sepsis related ruptured appendicitis caused by multi-drug resistant gram-negative bacteria including carbapenems. Our study's aim was to explore the clinical and non-clinical differences between Colistin+Tigecycline (Group I) and Colistin+Meropenem (Group II) in septic critically ill patients after perforated appendicitis during emergent surgical appendectomy.
**Methods:** A single-center observational retrospective study was processed in critical care unit at Prince Hamza hospital in Jordan between 1 Jan 2019 to 1 Jan 2021, Jordan. Comparative data were analyzed across the two tested groups using One-Sample T, Independent-T, and Chi Square Tests.
**Results:** Approximately 50 critical ill patients [54% Male and 46% Female] with an overall age of 58.4±9.95 years and an overall survival rate of 65% and 20% in Colistin/Tigecycline and Meropenem monotherapy, respectively.
**Conclusion:** In conclusion, the present study has shown that Tigecycline has a superior clinical positive impact than high dose Meropenem extended infusion when combined with the renal adjusted dose of Colistin.
**Key words:** Tigecycline, perforated appendicitis, Colistin, Carbapenem resistant, Meropenem, Enterobacteriaceae, mortality

## INTRODUCTION

Recently, there are emerging cases of sepsis related perforated appendicitis caused by multi-drug resistant - gram negative bacteria (MDR-GNB), including carbapenem resistant enterobacteria species (CRE). MDR-GNB involve bacteria which are resistant to at least 3 antibiotics, one of them comprise carbapenem beta-lactam antibiotics. Clinically, the incidence of mortality, morbidity, and high cost-expenditure rates from these offending bacteria are amazingly high (1,2). Mortality rates can be exponentially increasing the sepsis related perforated appendicitis, if the culprit bacteria are belonged to these carbapenems resistant enteric gram-negative bacteria, either the mechanism of resistant is originated from extended spectrum b-lactamases (ESBLs) over-expression plus porins modification, or the mechanism of resistant is totally related to carbapenemases hyper-production. Practically, CRE associated sepsis is often considered as

Received: 17.01.2022
Accepted: 25.03.2022

difficult to treat owing to limited number effective antibiotics (3-6).

Tigecycline is a glycylcycline antibiotic that is commonly used for skin and intra-abdominal infections. Of importance, Tigecycline considers as the most broad-spectrum antibiotic with susceptibility against many MDR-GNB, especially CRE species. Unfortunately, these interesting advantages are practically limited by the large volume of distribution and its bacteriostatic effects (7-9). Due to these Tigecycline pharmacokinetic /pharmacodynamic (PK/PD) barriers, Tigecycline has a higher mortality rate in septic patients compared with other ABs eventhough it has a full culture sensitivity. Tigecycline has the advantages of covering CRE but with limited clinical efficacy in septic critically ill patients due to its bacteriostatic activity. Theoretically, these clinically limited efficacy can be managed by doubling the standard dose, 200 mg loading dose followed by 100 mg BID instead of 100 mg loading dose followed by 50 mg twice daily (10-12). Although Meropenem is belonged to carbapenems, many emerging studies emphasized on its microbiologically efficacy by using high dose extended infusion strategy (e.g., 2 g Meropenem infused over 3 hours every 8 hours) as long as the minimum inhibitory concentration (MIC) of meropenem not exceeds 16 mcg/ml (13-15).

Colistin (Polymyxin E) is a polypeptide gram-negative active antibiotic which is universally considered as a lifesaving last resort chemotherapy for managing refractory cases of infections caused by pseudomonas. spp, acinentobacter.spp, and carbapenamase producing enterobacteriacae (CPE) species, especially in ventilator associated pneumonia (VAP) with accompanied septic shock status in intensive care units (ICU) (16-17). Carbapenems resistant enterobacteriacae (CRE), of particular the CPE generation like Klebsiella producing carbapenamase (KPC), are globally considered as an urgent difficult to treat infection. In cases of these CRE and CPE associated severe infection, Colistin is commonly used in combination with other adjunctive antibiotics, notably Tigecycline and Meropenem, to synergize Colistin and mitigate any risk of emerging resistant in situations of preserving these retricted antibiotics is of our critical priority. Entero-bacteriaceae species include enteric gram-negative bacteria that are belonged to Escherichia Coli, Klebsiella. Pneumoniae, Citrobacter, Provendicia, Morganella, and Enterobacter (18-19).

Our study's aim was to explore the clinical and non-clinical differences between Colistin+Tigecycline (Group I) and Colistin+ Meropenem (Group II) in septic critically ill patients after perforated appendicitis during emergent surgical appendectomy. regarding major clinical outcomes including overall ICU length of stay (LOS) and mortality.

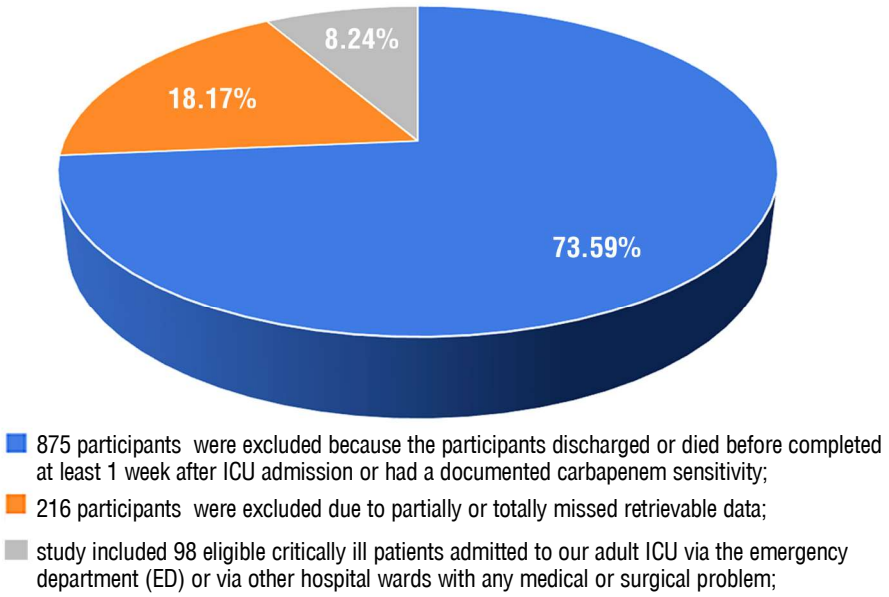
## MATERIALS AND METHODS

An observational retrospective study was processed in critical care unit at Prince Hamza hospital in Jordan between 1 Jan 2019 to 1 Jan 2021, Jordan, after it was approved by our institutional Review Board (IRB). Retrieving data of a total 1091 tested patients was processed from our electronic recording system (Hakeem). 875 patients were excluded from this study owing to full sensitivity of carbapenems, admission days <7 days, and missing retrievable data. Inclusion criteria in this study, including admitted patient from either emergency department or surgical ward who had a documented culture that indicated CRE and had a confirmed sepsis related perforated appendicitis. A flow chart for including and excluding icu participants was illustrated in *fig. 1*.

All CRE related sepsis blood samples were dually collected from peripheral and central lines. CRE species were identified using institutional VITEK 2, a fully auto-mated system that performs bacterial identification and antibiotic susceptibility testing, (Biomerieux Vitek 2 Compact Analyzer, Mild Steel, Digital, Automatic). While the bacterial identifications were conducted, Meropenem high dose extended infusion (maximally set to 2 g infused over 3 hours thrice daily) was initiated till clinical and biochemical signs of infection were abated or the results of antibiogram were known. If the affected bacteria were belonged to CRE, the clinical/ biochemical responses were exceeded 50%, and the MICs didn't exceed 16 mcg/ml, a loading doses of Colistin (5 mg/kg) followed by divided renal adjusted doses were initiated. Otherwise, if the clinical/ biochemical responses below 50% from baseline or the MICs exceeded 6 mcg/ml, Meropenem were immediately replaced by Tigecycline 50 twice daily, after 100 mg loading, and a loading dose of Colistin (5 mg/kg) followed by divided renal adjusted doses were initiated.

Patients' demographics, diagnostics, anthropometrics, hemodynamic, antibiotics durations, doses and responses, microbiological and antibiogram, length of stays, and mortalities data were recorded from Hakeem. The final 98 eligible patients were grouped into Colistin/Tigecycline group (Group I) or Meropenem monotherapy (Group II). All comparative tested variables were expressed as either Mean (SD) or Number (%) after analyzing by Independent-T and Chi Square tests, respectively, across the two compared groups.

**Figure 1 - Flow chart of the eligible studied critically ill patients**




## RESULTS

Totally, 98 ICU admitted patients [50 Male and 48 Female] with an overall age of 58.4±9.95 years were finally included in this study. Clinically, 33 tested patients (65%) from Group I were survivors which was significantly higher than in Group II (10 patients, 20%). Comparably, the critical and overall hospital admission days were substantially lesser in Group I versus Group II (7.93±0.26 days and 8.19±0.39 days vs 11.8±5.5 days 14.2±6.83 days, respectively).

Also, hemodynamic tested variables and albumin levels were significantly higher in Group I compared to Group II (115±0.66 mmHg, 69.9±0.66 mmHg, 84.9±0.66 mmHg, and -32.6%±15% vs 106±12.8 mmHg, 60.9±11.5 mmHg, 75.8±11.9 mmHg, and 28.8%±15%) for systolic, diastolic, and mean blood pressures, and percentage changes in albumin levels.

Pharmacokinetically, the average doses of Colistin and Meropenem that was investigated were 10.9±2.06 MIU/day for Group I versus 9.94±2.65 MIU/day for Group II compared to 5778±634 mg/day of Meropenem in Group II.

In contrast, the most significant differences in investigated outcomes' variables, particularly CRP to albumin levels (%ΔCRP: ALB), average norepinephrine rate (NEavg), and average body core temperature (Tavg) were in Group II compared to Group I (286%±301%, 37.7±1.28°C, and 7.99±5.72 μg/min vs 71.9%±16%, 36.8±0.07 °C, and 5.86±0.08 μg/min, respectively). All statistically analyzed comparative variables were included in *Tables 1, 2*.

## DISCUSSION

An identity study was conducted in 2010 in Russia. The efficacy and safety of tigecycline in patients with ruptured appendicitis was evaluated in a trial with meropenem in two multicenter, randomized, double-blind cardiac trials.

Patients (n=1642) aged 18 years or older with sepsis were stratified according to disease severity (APACHE II score ≤15 and >15 to <31 points) and randomized to receive either standard dose tigecycline (100 mg), first injection, starting with 50 mg 2 times a day i.v.), or meropenem (500 mg corresponds to 6 hours i.v.). In patients with impaired renal function, the dose of meropenem was adjusted over a period of 5–14 days. The primary endpoint was clinical response to therapy and cure (days 14–35 post-treatment).

In the microbiologically assessed patient population, the clinical cure rate was 86.1% in the tigecycline group and 86.2% in the meropenem group. When analyzed in a microbiologically modified intent-to-treat population of patients, the cure rate was 80.2% in the tigecycline group and 81.5% in the meropenem group.

When conducting a subgroup analysis after stratification of patients by the isolation of their pathogen in monoculture in comparison with the polymicrobial etiology of septic appendicitis, as well as depending on

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

| Variables | Total (N=98) | Group I* (N=50) | Group II** (N=48) | P-Value |
|---|---|---|---|---|
| Age (Yrs) | 58.4±9.95 | 56.6±8.13 | 59.7±10.1 | 0.01 (S) |
| Sex | | | | |
| F | 48 (46%) | 24 (48%) | 24 (50%) | 0.106 (NS) |
| M | 50 (54%) | 26 (52%) | 24 (50%) | |
| BW (Kg) | 73.9±9.32 | 72.3±8.84 | 74.2±10.2 | 0.07(NS) |
| BMI(Kg/m$^2$) | 25.7±3.74 | 25.3±3.26 | 25.9±3.99 | 0.11 (NS) |
| CRP1 (mg/dl) | 23.2±9.57 | 19.7±5.21 | 34.2±17.9 | 0.00 (S) |
| ALB1 (g/dl) | 2.65±0.18 | 2.63±0.16 | 2.75±0.32 | 0.00 (S) |
| CRP: ALB$_1$ | 7.09±3.06 | 5.99±1.85 | 10.24±5.90 | 0.00 (S) |
| %ΔALB | 29.3%±15% | 32.6%±15% | 28.8%±15% | 0.00 (S) |
| %ΔCRP: ALB | 106±%11% | 71.9%±16% | 286%±301% | 0.00 (S) |
| T$_1$ (°C) | 37.5±0.06 | 37.3±0.07 | 38.2±1.28 | 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) |
| ICU Stay day(s) | 10.12±0.32 | 7.93±0.26 | 11.8±5.5 | 0.00 (S) |
| Hospital Stay day(s) | 11.17±0.16 | 8.19±0.39 | 14.2±6.83 | 0.00 (S) |
| 28-day ICU Survival | 43(44%) | 33 (65%) | 10 (20.0%) | 0.00 (S) |
| 28-day ICU MOR | 55 (56%) | 17 (35%) | 38 (80.0%) | |

Data are presented as either Mean±SD by using Independent T-Test or as number (%) by using chi square test (at p-value $\leq$ 0.05).
* Critically ill patients on Colistin+Tigecycline. ** Critically ill patients on Colistin+Meropenem.

Decryptions:
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.
T - Temperature.
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.
MOR - Mortality.

the specific nosologically form of the disease, between groups treated with tigecycline and meropenem, statistically significant differences in the frequency of clinical cure were noted did not have. Which differs from the results of our study, which was 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-

**Table 2 - Comparison of microbiological and antibiotic data among the two tested groups**

| Variables | Total (N=98) | Group I* (N=50) | Group II** (N=48) | P-Value |
|---|---|---|---|---|
| EMP ABs 1st 3-4 days | | | | |
| CFP | 24 (24%) | 14 (28%) | 10 (21%) | 0.110 (NS) |
| PIP/TAZ | 24 (24%) | 10 (20 %) | 14 (29 %) | |
| MER | 22 (22%) | 10 (20 %) | 12 (25%) | |
| IMP/CIL | 28 (30%) | 16 (32 %) | 12 (25 %) | |
| CrCl (ml/min) | 48.3±44.64 | 103±75.9 | 64.6±20.3 | 0.00 (S) |
| Meropenem (mg/day) | 5778±634 | 0.00±0.00 | 5778±634 | 0.00(S) |
| Colistin (MIU/day) | 10.23±4.93 | 10.9±2.06 | 9.94±2.65 | 0.00(S) |
| CRE-E. Coli | 20 (20 %) | 12(24 %) | 8(17 %) | |
| CRE-K. P | 20 (20 %) | 6(12 %) | 14(29 %) | |
| CRE-E.spp | 24 (24%) | 8(16 %) | 16 (33 %) | |
| CRE-P.spp | 21 (21 %) | 14(28 %) | 7 (15 %) | |
| CRE-C.spp | 13 (15%) | 10(20 %) | 3 (6 %) | |

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

Decryptions:
* Critically ill patients on Colistin+Tigecycline. ** Critically ill patients on Colistin+Meropenem. N - Number of studied critically ill patients. MDR - Multidrug-resistant. HC - Hydrocortisone. AB - Antibiotics. CrCl - Creatinine clearance. MIU - Millimillion unit. PIP/TAZ - Piperacillin/Tazobactam. MER - Meropenem. IMP/CIL - Imipenem/Cilastatin. 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.

volume unit, so our data may be useful in other centers. A larger, multisite, and prospective study is needed to control for multiple confounders.

## CONCLUSION

The present study has shown that Tigecycline has a superior clinical and biological positive impact than high dose Meropenem extended infusion when combined with the renal adjusted dose of Colistin for rupture appendicitis associated sepsis in critically ill patients.

### *Conflict of interest*

The author declare that he has no conflict of interest.

### *Ethical approval*

Ethical approval was obtained.

## REFERENCES


1. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. London, UK: Review on Antimicrobial Resistance. 2016.
2. Mullard A. Tackling antimicrobial drug resistance. Nat Rev Drug Discov. 2016;15(6):375.
3. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother. 2010;54(3):969-76.
4. Badal RE, Bouchillon SK, Lob SH, Hackel MA, Hawser SP, Hoban DJ. Etiology, extended-spectrum beta-lactamase rates and antimicrobial susceptibility of gram-negative bacilli causing intra-abdominal infections in patients in general pediatric and pediatric intensive care unit's global data from the Study for Monitoring Antimicrobial Resistance Trends 2008 to 2010. Pediatr Infect Dis J. 2013;32(6): 636-40.
5. Bordier M, Uea-Anuwong T, Binot A, Hendrikx P, Goutard FL. Characteristics of One Health surveillance systems: a systematic literature review. Prev Vet Med 2018. [Epub ahead of print].
6. Calba C, Goutard FL, Hoinville L, Hendrikx P, Lindberg A, Saegerman C, et al. Surveillance systems evaluation: a systematic review of the existing approaches. BMC Public Health 2015;15:448.
7. Aenishaenslin C, Heasler B, Ravel A, Parmley J, Stark K, Buckeridgee D. Evidence needed for antimicrobial resistance surveillance systems. Bull World Health Organ. 2019;97(4):283-289.
8. Azimi L, Lari AR. Colistin-resistant Pseudomonas aeruginosa clinical strains with defective biofilm formation. GMS Hyg Infect Control. 2019;14:Doc12. eCollection 2019.
9. Borgatta B, Gattarello S, Mazo C A, Imbiscuso A T, Larrosa M N, Luján M, et al. The clinical significance of pneumonia in patients with respiratory specimens harboring multidrug-resistant Pseudomonas aeruginosa: a 5-year retrospective study following 5667 patients in four general ICUs. Eur J Clin Microbiol Infect Dis. 2017;36(11): 2155-2163.
10. Castanheira M, Deshpande LM, Costello A, Davies TA, Jones RN. Epidemiology and carbapenem resistance mechanisms of carbapen-emnon-susceptible Pseudomonas aeruginosa collected during 2009-11 in 14 European and Mediterranean countries. J Antimicrob Chemother. 2014;69(7):1804-14.
11. Chen B-y, He L-x, Hu B-j. Chinese Expert Consensus for the Diagnosis, Treatment, Prevention and Control of Acinetobacter Baumannii. Zhonghua Yi Xue Za Zhi. 2012;92(2):76-85. Chinese
12. Chen S, Hu F, Zhang X, Xu X, Liu Y, Zhu D, et al. (2011). Independent emergence of colistin-resistant Enterobacteriaceae clinical isolates without colistin treatment. J Clin Microbiol. 2011;49(11):4022-3.
13. Chopra T, Marchaim D, Awali RA, Krishna A, Johnson P, Tansek R, et al. Epidemiology of bloodstream infections caused by Acinetobacter baumannii and impact of drug resistance to both carbapenems and ampicillin-sulbactam on clinical outcomes. Antimicrob Agents Chemother. 2013;57(12):6270-5.
14. Schwaber MJ, De-Medina T, Carmeli Y. Epidemiological interpreta-tion on antibiotic resistance studies – what are we missing? Nat Rev Microbiol. 2004;2(12):979-83.
15. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2(2):CD003543.
16. Ansari F, Gray K, Nathwani D, Phillips G, Ogston S, Ramsay C, et al. Outcomes of an intervention to improve hospital antibiotic prescribing; interrupted time series with segmented regression analysis. J Antimicrob Chemother. 2003;52(5):842-8.
17. Solomon DH, Van Houten L, Glynn RJ, Baden L, Curtis K, Schrager H, et al. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. Arch Intern Med. 2001; 161(15):1897-902.
18. Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. Ann Clin Microbiol Antimicrob. 2017;16(1):18.
19. Dellit TH, Owens RC, McGowan Jr JE, Gerding DN, Weinstein RA, Burke JP, et al. Infectious diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for developing an Institutional Program to Enhance Antimicrobial Stewardship. Clin Infect Dis. 2007;44(2):159-77.