Mortality Outcomes associated with Meropenem Front-Loading Dose in Critically Ill Septic Patients with Acute Kidney Injury

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ABSTRACT

Introduction:

In acute kidney injury (AKI), increased volume of distribution (Vd) may reduce therapeutic drug concentrations. Appropriate antimicrobial dosing is crucial to maximise microbial killing. Meropenem front-loading dose, defined as administering the full dose unchanged during the first 24 hours. This study aimed to evaluate the clinical outcomes such as survival, Intensive Care Units (ICU) / hospital length of stay (LOS) and duration of mechanical ventilation as well as the safety profile of meropenem front-loading dose in critically ill septic patients with AKI.

Methods:

A prospective, multicenter, observational study was conducted across 15 ICU in Malaysia. Adult patients diagnosed with sepsis who received at least 72 hours of meropenem treatment, with or without a front-loading dose, between May 2017 and May 2018 were included. Patients were monitored throughout their ICU stay, and all data were collected using a standardized data collection form. Data were analysed descriptively and univariate analysis was performed to assess associations and differences between groups.

Results:

A total of 78 patients were treated with meropenem. On average, the patients were 53.1 (SD=15.1) years of age, predominantly male (n=50, 64.1%) and admitted from medical unit (n=41, 52.5%). Majority of patients were treated with meropenem empirically (n=54, 69.2%). The most prevalent infection types were community-acquired pneumonia (n=13, 16.7%) and hospital acquired/ventilator-associated pneumonia (n=11, 14.1%). *Klebsiella pneumoniae* (n=10, 12.8%) and *Pseudomonas aeruginosa* (n=4, 5.1%) were the most common bacterial infections encountered. Although statistically insignificant, patients treated with meropenem front-loading dose had lower mortality than patients treated without meropenem front-loading dose (38.7% vs 44.7%, *P*=0.601). Similarly, the meropenem front-loading dose group showed shorter ICU/hospital LOS and duration of mechanical ventilation. No adverse effects related to meropenem were reported.

Conclusion:

The study highlighted the potential impact of meropenem front-loading dose in reducing ICU mortality, ICU/hospital LOS, and duration of mechanical ventilation, although these differences were not statistically significant. Optimizing antimicrobial dosing in critically ill patients with AKI remains crucial, and further research is needed to confirm its clinical benefits.

Keywords:

Meropenem, front-loading dose, critically ill, intensive care unit

INTRODUCTION

Acute kidney injury (AKI) occurred in 40–50% of patients in intensive care units (ICU).[1] The prevalence of sepsis-related AKI was 16.3%.[2] About one in three sepsis patients develop AKI, with sepsis-associated AKI leading to an estimated 6 million AKI cases globally each year, or nearly 1 per 1000 people.[3] AKI is defined by the presence of any one of the following criteria: an increase in serum creatinine by 0.3 mg/dL or more within 48 hours; an increase in serum creatinine to 1.5 times or more than the baseline (known or presumed to have occurred within the prior 7 days); or urine output of less than 0.5 mL/kg/h for at least six consecutive hours.[4]

Pathophysiological changes in critically ill patients can affect the pharmacokinetic (PK) and pharmacodynamic (PD) properties of medications.[5] Administering drug doses to critically ill patients with AKI are complex due to the dynamic changes in renal function, including fluctuations in volume status, which are difficult to quantify. Therefore, it is necessary to frequently reassess drug dosages in this population.[6]

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[7] In the Intensive Care Units (ICU), sepsis diagnosis relies on early recognition of symptoms and signs. Key indicators include confusion, hypoxia, hypotension, pyrexia, tachycardia, tachypnea, and leukocytosis.[8] In sepsis and septic shock, vasodilation and increased vascular permeability cause capillary leak syndrome, which expands the volume of distribution (Vd) for antimicrobials like beta-lactams and aminoglycosides. Without administering higher initial doses, reaching therapeutic serum concentrations may be delayed. Moreover, augmented renal clearance characterized by glomerular hyperfiltration accelerates drug elimination, further risking subtherapeutic levels.[5]

An increase in Vd and clearance observed in the early phase of sepsis can affect the dosing of hydrophilic antibiotics. Therefore, initial antibiotic dosing needs to account for the increased Vd seen in critically ill patients with multiorgan dysfunction syndrome. Roberts et al. concluded that 70% of the patients did not achieve desired antibiotic concentrations in the early phase of antibiotic therapy when dosing increment was required.[10] A multicentre study by Taccone et al. reported on the inadequate conventional initial dosing for various beta-lactam agents in critically ill patients where PK/PD targets were not achieved during the first day of therapy. [11] In this study, 28% of the patients on ceftazidime, 16% on cefepime, and 44% on piperacillin/tazobactam met the PK/PD targets on the first day of antibiotic initiation. Consequently, these studies highlighted the importance of considering higher-than-standard doses or a front-loading dose during the initial phase of therapy, due to PK and PD variations.[10–12] Administering front-loading doses of meropenem during the initial 24 hours of treatment should consider the expected increases in the antibiotic's Vd.[12]

Meropenem is a hydrophilic antibiotic that is mainly cleared by the kidneys. In patients with AKI, reduced renal function decreases drug clearance, leading to higher blood concentrations and increased exposure. The elevated exposure raises the risk of toxicity which may include neurological issues, further kidney function deterioration, liver injury and blood abnormalities such as thrombocytosis.[13,14] Consequently, dosing adjustments and careful monitoring are essential in patients with AKI to prevent drug accumulation while achieving effective antimicrobial therapy.[5,15]

The adverse drug reactions associated with meropenem can be identified through neurological assessments, as well as serial monitoring of laboratory data including liver and renal function tests and complete blood counts. Elevated meropenem levels especially in patients with impaired renal clearance, are linked to adverse reactions such as neurotoxicity (e.g., confusion, seizures) and potential nephrotoxicity as observed by Imani et al..[14] Regular neurological assessments and serial monitoring of liver and renal function tests as well as complete blood counts monitoring can help distinguish these drug-induced effects from symptoms of the underlying illness.[14] Hence, this study was designed to evaluate the impact of the front-loading dose strategy of meropenem in critically ill AKI patients in the ICU, focusing on clinical outcomes such as ICU mortality, ICU and hospital length of stay (LOS), duration of mechanical ventilation, and the safety of this dosing approach in septic patients with AKI.

METHODS

Study Design

A prospective, multicentre, observational study was conducted across 15 ICU (Supplementary File 1) in Malaysia; including 2 ICU in East Malaysia and 13 ICU in West Malaysia. All participating ICU primarily treated adult patients from both medical and surgical disciplines. General ICU admitted a mix of patients from both specialties whereas medical ICU focused exclusively on patients with medical-related illnesses. Critically ill patients admitted between May 2017 and May 2018 were included in the study. Patient identification was carried out using the ICU census and those prescribed meropenem were identified through the inpatient pharmacy database.

Study Population

All adult patients more than 18 years of age with AKI who had been diagnosed with sepsis or septic shock admitted between May 2017 and May 2018 in the 15 ICU included in the study and were treated with intravenous meropenem for at least 72 hours were screened for potential recruitment into the study. Patients who had acute on chronic kidney injury, end-stage renal failure (ESRF), sepsis with meningitis and those who received meropenem other than intravenous route of administration were excluded. These exclusions were made because meropenem dosing can vary significantly in these conditions, either requiring higher doses (e.g., meningitis) or lower doses (e.g., ESRF), potentially introducing variability that could affect the study outcomes.

Definitions

According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines, AKI is defined by the presence of at least one of the following criteria: an increase in serum creatinine by 0.3 mg/dL or more within 48 hours, an increase in serum creatinine to 1.5 times or more above baseline (either known or presumed to have occurred within the previous seven days), or urine output of less than 0.5 mL/kg/h for at least six consecutive hours. According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is defined as a dysregulated host response to infection leading to life-threatening organ dysfunction, characterized by an increase in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points.

Septic shock represents a more severe subset of sepsis, distinguished by persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) of ≥65 mmHg and a serum lactate concentration >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation. This condition reflects profound circulatory, cellular, and metabolic abnormalities that contribute to increased mortality risk.

Meropenem front-loading dose was defined as the dose of meropenem given unchanged during the first 24 hours of therapy whereas, without meropenem front-loading dose group received meropenem based on estimated creatinine clearance during the first 24 hours of therapy.

Data Collection

All critically ill patients admitted to the ICU during the study period were screened for study eligibility and recruited in the study if they fulfilled all the inclusion criteria. Subsequently, a data collection form was used to collect all research data. All data

were obtained through patient's case note, laboratory report and drug charts. Patients were followed up during their ICU stay for a maximum of 28 days.

For patient demographic data, data such as age, weight, height, gender, race, date of hospital admission, date of ICU admission, co-morbidities, diagnosis, concomitant nephrotoxic drug, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score and presence of vasoactive agents (Noradrenaline, Dobutamine, Dopamine, Vasopressin) were recorded. These data were obtained from patients' case note and laboratory reports. Both APACHE-II score and SOFA score were commonly used to assess prognosis and predicting mortality in critically ill patients. Higher SOFA scores are associated with increased organ system failure (neurological, respiratory, cardiovascular, renal, hepatic, and hematologic) and higher APACHE II is an indication of higher mortality risk.

Meropenem related data were also recorded. This included with/without meropenem front-loading dose administration, dose, duration of therapy, indication, types of infections, microorganism and whether there were other concomitant antibiotics given to patients.

For meropenem safety data, data recorded were serum creatinine, estimated creatinine clearance (Cockcroft-Gault equation), urine output and whether patients received any renal replacement therapy (RRT). Patients were monitored for any negative effects associated with elevated meropenem levels, including neurotoxicity (e.g., confusion, seizures) and possible nephrotoxicity. The study investigators routinely monitored full blood counts, liver and renal function tests, and neurological function to differentiate between drug-induced side effects and symptoms of the underlying illness.

Lastly, clinical outcomes data which included resolution of infection (temperature <38.3°C for more than 24 hours, white blood cells (WBC) count <11,000/mm^3 or decrease by 25% of maximal value, C-Reactive Protein (CRP) level), duration of mechanical ventilation, duration of ICU stay, duration of hospital stay and ICU mortality (dead/alive) were also collected.

Outcome Measurement

The primary outcome was ICU mortality, defined by whether the patient is alive or deceased at the point of transfer to another ward. For patients transferred out from the ICU, we do not collect any additional survival data after their transfer. The secondary outcome was ICU/Hospital LOS, duration of mechanical ventilation and the safety profile of meropenem front-loading dose therapy. ICU LOS is calculated from the time of ICU admission until the patient is transferred out to another ward. In contrast, hospital LOS is defined as the total duration from hospital admission to discharge, thereby including any time spent in other ward before or after the ICU stay. The safety profile of administering meropenem front-loading dose was assessed daily for adverse events. Study investigators were required to provide an assessment of whether any reported adverse event was considered related to the study treatment.

Statistical Analysis

Data was initially transcribed into a Microsoft Excel Spreadsheet by an experienced researcher before being transferred to STATA 12.0 (StataCorp, College Station, TX, USA) for data analysis.[15] Data was checked for normality and those distributed normally were presented as mean and standard deviation (SD), and those not distributed normally as median and interquartile range (IQR). Before conducting univariate analysis, data was explored to check for any errors and incorrect data entry. Both descriptive and univariate statistical analysis were conducted where appropriate. Categorical data was tabulated using contingency table and Pearson's chi-square test was used to find any potential association. Comparisons between the study groups were conducted using either the independent *t*-test or Mann-Whitney test as appropriate. All probability values were two-sided and a *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Study Participants

A total of 78 patients met the inclusion criteria during the study period. Of these, 31 patients received meropenem front-loading dose, while 47 patients did not.

Patient Demographics

Patients' baseline characteristics, co-morbidities and indications of meropenem therapy are shown in Table 1. Baseline characteristics did not differ between the 2 groups except for weight and body mass index (BMI). Patients with meropenem front-loading dose have lower weight (median 60kg vs 70kg, *P*=0.029) and BMI (24.2kg/m^2 vs 25.6kg/m^2, *P*=0.037). Overall, the mean age was 53.1 years old, and the majority of patients were male (64.1%). The ethnics distributions were: Malay (69.2%), Chinese (19.4%), Indian (6.4%), and 6.4 % from other races. The main cause of ICU admission was medical related illnesses (52.5%) rather than surgical cases (47.4%). The SOFA score and APACHE-II were similar (mean SOFA score=10.6, mean APACHE-II score=25.5). Diabetes (35.9%) and hypertension (30.8%) were the two most common co-morbidities. Infections requiring meropenem therapy were community-associated pneumonia (16.7%), hospital acquired pneumonia or ventilator-associated pneumonia (14.1%), urinary tract infection (11.5%), skin and soft tissue infection (11.5%), melioidosis (10.3%), and peritonitis (10.3%) (Table 2).

Klebsiella pneumonia was the most commonly isolated pathogen (12.8%), followed by *Pseudomonas aeruginosa* (5.1%) and *Enterobacter spp*. (3.9%). Approximately 60% of the culture and sensitivity tests showed no growth, indicating that

Table 1. Patient baseline characteristics (n=78)

Characteristic	Front-Loading Dose (n=31)	Without Front-Loading Dose (n=47)	Statistic (df)	*P*-value
Age (years), mean (SD)	53.7 (13.0)	52.5 (16.5)	-0.34 (76)	0.732[a]
Height (cm), mean (SD)	161.2 (7.7)	163.1 (6.4)	1.21 (76)	0.230[a]
Weight (kg), median (IQR)	60 (50, 70)	70 (60, 80)	2.17	0.029[b]
BMI (kg/m²), median (IQR)	24.2 (21.1, 26.1)	25.6 (24, 28.6)	2.08	0.037[b]
Gender, n (%)				
Male	17 (54.8)	33 (70.2)	1.92 (1)	0.166[c]
Female	14 (45.2)	14 (29.7)		
Ethnicity, n (%)				
Malay	19 (61.3)	35 (74.5)	-	0.153[d]
Chinese	7 (22.6)	7 (14.9)		
Indian	4 (12.9)	1 (2.1)		
Others	1 (3.2)	4 (8.5)		
Co-morbidities, n (%)*				
Hypertension	11 (35.5)	13 (27.7)	0.54 (1)	0.464[c]
Diabetes	10 (32.3)	18 (38.3)	0.30 (1)	0.586[c]
Dyslipidemia	2 (6.5)	1 (2.1)	-	0.560[d]
Chronic obstructive pulmonary disease	2 (6.5)	3 (6.4)	-	1.000[d]
Ischemic heart diseases	2 (6.5)	3 (6.4)	-	1.000[d]
Asthma	2 (6.5)	0 (0)	-	0.155[d]
Deep vein thrombosis	2 (6.5)	0 (0)	-	0.155[d]
CVA	1 (3.2)	1 (2.1)	-	1.000[d]
Others	6 (19.4)	6 (12.8)	0.62 (1)	0.430[c]
Renal profile				
Serum Creatinine (mmol/L), median (IQR)	268 (140, 350)	250 (168, 424)	0.54	0.592[b]
Admission, n (%)				
Medical	16 (51.6)	25 (53.2)	0.02 (1)	0.891[c]
Surgical	15 (48.4)	22 (46.8)		
SOFA score, mean (SD)	10.4 (4.5)	10.7 (4.2)	0.37 (76)	0.714[a]
APACHE 2 score, mean (SD)	25.2 (8.4)	25.7 (8.2)	0.24 (70)	0.814[a]

[a]Independent t test, [b]Mann-Whitney U test, [c]Pearson's Chi Square Test, [d]Fisher's Exact Test

Abbreviation: cm; centimetres, kg; kilogram, BMI; Body Mass Index, SOFA; Sequential Organ Failure Assessment, APACHE; Acute Physiologic Assessment And Chronic Health Evaluation, SD; Standard Deviation, IQR; Inter-Quartile range

*the total percentage is more than 100% (n>78) as the patients had more than one co-morbidity

69.2% of meropenem treatments were empirical (Table 3).

Patients who received meropenem front-loading dose had a shorter median duration of meropenem treatment compared to patients without a meropenem front-loading dose (median 5 vs 7 days, *P*=0.363). Patients with meropenem front-loading dose received significantly higher total dose compared to those without meropenem front-loading dose (37.5g vs 15g, *P*=<0.001).

Approximately 46.2 % (n = 36) of patients received multiple antibiotic therapy, with the majority from the group without meropenem front-loading dose (27 vs 9, *P*=0.014). A total of 10.3% (n = 8) received concomitant nephrotoxic drugs. Despite having AKI, only 56.4% (n=44) required RRT during meropenem treatment (Table 4).

Safety Profile

In the meropenem front-loading dose group (n=31), the median baseline serum creatinine before treatment was 268 mmol/L, which slightly increased to 280 mmol/L after treatment completion. Despite the increase, urine output remained stable at approximately 0.4mL/kg/h.

A reduction in total WBC count, temperature, AST, ALT, and bilirubin were observed following the administration of meropenem. In patients with adjusted meropenem dosing, the median baseline serum creatinine was 250 mmol/L which reduced to 205 mmol/L after completing the treatment. Improvement in urine output, total WBC count, temperature, and ALT were also noted (Table 5).

Clinical Outcomes

ICU mortality was lower in patients who received meropenem front-loading dose compared to those who did not (38.7% vs 44.7%, *P*=0.601) (Table 6). ICU and hospital LOS were shorter in patients with meropenem front-loading dose (11 vs 13 days, *P*=0.923; and 19 vs 21 days, *P*=0.550 respectively). However, all the differences were not statistically significant. Median duration of mechanical ventilator was also similar between the two groups.

Table 2. Meropenem indication (n=78)

Indications	Front-Loading Dose (n=31)	Without Front-Loading Dose (n=47)	Statistic (df)	*P*-value
Community associated pneumonia	9 (29.1)	4 (8.5)	5.66 (1)	0.017[a]
Hospital acquired pneumonia / Ventilator-associated pneumonia	2 (6.5)	9 (19.2)	2.48 (1)	0.115[a]
Urinary tract infection	2 (6.5)	7(14.9)	1.31 (1)	0.253[a]
Skin and soft tissue infection	0 (0)	9 (19.2)	6.71 (1)	0.010[a]
Melioidosis	5 (16.1)	3 (6.4)	-	0.254[b]
Peritonitis	2 (6.5)	6 (12.8)	-	0.467[b]
Biliary sepsis	2(6.5)	3 (6.4)	-	1.000[b]
Bacteremia	2 (6.5)	2 (4.3)	-	1.000[b]
Intraabdominal Infection	2 (6.5)	2 (4.3)	-	1.000[b]
Leptospirosis	0 (0)	3 (6.4)	-	0.272[b]
Aspiration pneumonia and lung abscess	1 (3.2)	1 (2.1)	-	1.000[b]
Acute infective pancreatitis	1 (3.2)	1 (2.1)	-	1.000[b]
Catheter related bloodstream infection	2 (6.5)	0 (0)	-	0.155[b]
Acute infective diarrhea	1 (3.2)	0 (0)	-	0.397[b]

[a]Pearson's Chi Square Test, [b]Fisher Exact Test

Table 3. Types of cultured organism (n=78)

Microorganism, n (%)	Total, n (%)
Klebsiella pneumonia	10 (12.8)
Pseudomonas aeruginosa	4 (5.1)
Enterobacter	3 (3.9)
Staphylococcus aureus	1 (1.3)
None	45 (57.7)
Others	15 (19.2)

Table 4. Meropenem treatment regime (n=78)

Characteristics	Front-Loading Dose (n=31)	Without Front-Loading Dose (n=47)	Statistic (df)	*P*-value
Treatment, n (%)				
Empirical	20 (64.5)	34 (72.3)	0.54 (1)	0.464[a]
Definitive	11 (35.5)	13 (27.6)		
Duration of therapy, median (IQR)	5 (4, 10)	7 (4, 9)	0.91	0.363[b]
Meropenem Maintenance Dose, n (%)				
500mg every 24 hour	0	1 (2.1)	-	<0.001[c]
500mg every 12 hour	0	11 (23.4)		
1g every 24 hour	1 (3.2)	3 (6.4)		
1g every 12 hour	2 (6.5)	26 (55.3)		
1g every 8 hour	28 (90.3)	5 (10.6)		
Others	0	1 (2.1)		
Total Dose(mg/kg/day), median (IQR)	37.5 (15, 50)	15 (8, 28.57)	-3.478	<0.001[b]
Number of Patients with Concomitant Antibiotic	9 (29)	27 (57.5)	6.07 (1)	0.014[a]
Renal replacement therapy during treatment	16 (51.6)	28 (59.6)	0.48 (1)	0.488[a]
Concomitant nephrotoxic antibiotic	2 (6.5)	6 (12.8)	-	0.467[a]

[a]Independent t test, [b]Mann-Whitney U test, [c] Pearson's Chi Square Test, [d]Fisher's Exact Test
Abbreviations: IQR; Inter-Quartile Range

Table 5. Monitoring parameter during meropenem therapy (n=78)

Parameters	Front-Loading Dose (n=31)		Without Front-Loading (n=47)	
	Before	After	Before	After
Serum Creatinine (mmol/L), median (IQR)	268 (140, 350)	280 (95, 423)	250 (168, 424)	205 (108, 392)
Creatinine Clearance (mL/min), median (IQR)	25 (20, 36.8)	23 (17, 61.2)	26.1 (16.2, 39.9)	30 (17.7, 68)
Urine Output (mL/kg/h), median (IQR)	0.4 (0.01, 1)	0.4 (0, 0.9)	0.4 (0.1, 1)	0.7 (0.3, 1.6)
Temperature (^oC), mean (SD)	37.5 (1.4)	37 (0.9)	37.9 (1.3)	37.1 (1.2)
WBC ($x10^3/mm^3$), mean (SD)	23 (12.2)	16.2(7.8)	21.2 (10.6)	15.8 (8.5)
Bilirubin (µmol/L), median (IQR)	27.7 (11, 82)	26 (12, 69)	27 (12.2, 52)	19 (11, 52)

Table 5. Continued

Parameters	Front-Loading Dose (n=31)		Without Front-Loading (n=47)	
	Before	After	Before	After
AST (U/L), median (IQR)	120.5 (53.5, 222)	101 (36, 258)	70 (44, 212)	90 (40.5, 201.5)
ALT (U/L), median (IQR)	56 (28, 118)	51 (15, 96)	55 (22, 127)	40 (23, 113)
ALP (U/L), median (IQR)	124 (84, 157)	145.5 (98, 207.5)	118 (75, 166)	126 (84, 193)
CRP (mg/L), median (IQR)[a]	199 (153, 291.2)	99.9 (91.7, 120.9)	156 (55.3, 291.4)	83.9 (26.5, 170.7)

Abbreviations: IQR; Inter-Quartile Range, SD; Standard Deviation, WBC; White Blood Cells, AST; Aspartate Transaminase, ALT; Alanine Transaminase, ALP; Alkaline Phosphatase.
[a] CRP values for Meropenem front-loading dose (n=45), Without front-loading (n=34)

Table 6. Clinical outcomes (n=78)

Characteristics	Front-Loading Dose (n=31)	Without Front-Loading Dose (n=47)	Statistic (df)	*P*-value
ICU length of stay (days), median (IQR)	11 (7, 25)	13 (7, 21)	0.09	0.923[a]
Hospital length of stay (days), median (IQR)	19 (15, 39)	21 (14, 31)	-0.59	0.550[a]
Mechanical ventilation duration (days), median (IQR)	9 (7, 25)	11 (7, 16)	-0.03	0.979[a]
ICU mortality, n (%)				
Dead	12 (38.7)	21 (44.7)	0.27 (1)	0.601[b]
Alive	19 (61.3)	26 (55.3)		

[a]Mann-Whitney U test, [b]Pearson's Chi Square Test
Abbreviations: IQR; Inter-Quartile Range

DISCUSSION

In this study, the mean age was 53.1 years old which was older compared to other studies where the mean age was the 40s.[16,17] Gender and race were similar to a surveillance study previously done in Malaysia[16] and was also in accordance with the annual registry report in which the patients were often male and Malay.[18] The APACHE-II score in our subjects predicted 50% mortality (mean (SD): 25.5 (8.2)).[10] Distinct co-morbidities such as hypertension, diabetes, and ischemic heart disease along with AKI and sepsis, increased the prediction of mortality and length of ICU stay.[19,20] More than a third of our subjects have co-morbidities such as diabetes and hypertension which affected their prediction of mortality.

The study found that the practice of meropenem front-loading dose was used in 6 out of 15 ICU enrolled for data collection. ICU without the practice of meropenem front-loading dose, relied on references of dose adjustments in patients with stable chronic kidney disease (CKD). This practice aimed at maintenance therapies, which are given on a long-term basis to individuals with CKD; but, it could exaggerate the necessary dose reductions for those experiencing AKI.[13] The pharmacokinetics of meropenem are primarily affected by renal clearance. In patients with normal to mildly reduced renal function, typical dosing appears to be adequate.[14] However, patients with renal impairment may have prolonged meropenem half-life up to about 10 times longer compared to patients with normal renal function.[15] In our study, our subjects had reduced renal function with calculated creatinine clearance of less than 30mL/min and with inadequate urine output of 0.4 mL/kg/h. Thus, they may have prolonged clearance of meropenem. It was observed that patients with meropenem front-loading dose had lower mortality, but shorter ICU LOS, shorter time on mechanical ventilation and shorter hospital LOS, the differences were not statistically significant.

Patients who received a meropenem front-loading dose had a significantly higher total dose of meropenem compared to patients with adjusted dose. Despite the higher dosing, there were no significant adverse events, such as neurologic complications reported. The meropenem doses used in this study remained within the recommended daily maximum of 3 g/day. Front-loading of meropenem can cause a temporary rise in serum creatinine without damaging the kidneys.[5] The higher dose may alter kidney blood flow or the way the drug is cleared which can briefly increase creatinine levels. Additionally, common issues in septic patients such as dehydration or muscle wasting can also contribute to higher creatinine.[21]

Despite the rise, overall kidney function (as measured by urine output) remained unchanged, suggesting that the increase is a transient effect rather than true nephrotoxicity.

Limitations of the study

The study had several limitations. Firstly, the small cohort size and heterogeneity of the study population, including variations in meropenem dosing regimens and renal function may have affected the findings. However, the study provided real-world data from a diverse cohort of septic ICU patients, specifically those with AKI but without CKD. Secondly, the study was not randomized, and the

choice between front-loading and adjusted dosing was determined at the discretion of the treating physicians, potentially introducing selection bias.

CONCLUSION

Although not statistically significant, lower ICU mortality, reduced ICU and hospital LOS and shorter duration of mechanical ventilation were observed in patients receiving front-loading dose meropenem. In critically ill patients with AKI, this dosing strategy may be a viable approach. However, further well-designed studies are required to rigorously assess its clinical efficacy and safety.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICAL APPROVAL

This research was registered with the National Medical Research Registry (NMRR), and approved by the Medical Research & Ethics Committee, Ministry of Health Malaysia (NMRR-16-2798-33127) on 23 August 2017.

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SUPPLEMENTARY FILE 1

Participating ICU:

1. Hospital Tengku Ampuan Afzan, Kuantan
2. Hospital Pulau Pinang, Pulau Pinang
3. Hospital Raja Permaisuri Bainun, Ipoh, Perak
4. Hospital Sultanah Aminah, Johor Bahru, Johor
5. Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu
6. Hospital Sungai Buloh, Selangor
7. Hospital Queen Elizabeth, Kota Kinabalu, Sabah
8. Hospital Raja Perempuan Zainab 2, Kota Bahru, Kelantan
9. Hospital Kuala Lumpur, Kuala Lumpur
10. Hospital Tuanku Jaafar, Seremban
11. Hospital Selayang, Selangor
12. Hospital Tuanku Fauziah, Kangar, Perlis
13. Hospital Taiping, Perak
14. Hospital Teluk Intan, Perak
15. Hospital Tengku Ampuan Rahimah, Klang, Selangor