The Occurrence of Acute Kidney Injury (AKI) in Intensive Care Unit (ICU) Patients Treated with Piperacillin/Tazobactam and Meropenem – an Observational Study

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Abstract

Introduction: Piperacillin/Tazobactam was seen to be associated with increased acute kidney injury (AKI) and exhibited delayed improvement in serum creatinine level during antibiotic therapy. Among the intensive care unit (ICU) patients, however, the evidences were conflicting with non-critically ill patients.
Objective: To compare AKI development or delayed renal recovery during therapy or after completion of therapy in adult critically ill patients who received Piperacillin/Tazobactam or Meropenem.
Method: This was a retrospective observational study. All eligible adult patients treated with Piperacillin/Tazobactam or Meropenem in ICU at Hospital Sultanah Aminah Johor Bahru from January 2015 – June 2018 were included in the study. The patients were followed up until the completion or discontinuation of antibiotic, transferred out from ICU or died. Paired sample t-test was performed to compare the renal recovery in both groups from the initiation of antibiotic to the last day of follow up.
Results: A total of 232 patients were included in the study, with 120 patients in the Piperacillin/Tazobactam group and 112 patients in the Meropenem group. Comparable occurrence of AKI was observed in the Piperacillin/Tazobactam and Meropenem group on the initiation of antibiotic treatment (55.8%, n=67 vs 65.2%, n=73; p=0.146) and last day of follow up (56.7%, n=68 vs 54.5%, n=61; p=0.7). Significant improvement of creatinine clearance (CrCl) in Meropenem group from the first to last day of antibiotic treatment was observed (mean CrCl 55.16 ml/min (SD 51.14) to 83.01 ml/min (SD 108.48), $p<0.05$), but not in Piperacillin/Tazobactam group (mean CrCl 66.79 ml/min (SD 63.82) to 72.66 ml/min (SD 66.24), p=0.149), indicating a delayed renal recovery in patients receiving Piperacillin/Tazobactam.
Conclusion: The occurrence of AKI in the Piperacillin/Tazobactam group was comparable with the Meropenem group but renal recovery in the Piperacillin/Tazobactam group was delayed compared with Meropenem group at the last day of follow up.
Keywords: Acute kidney injury, renal recovery, critically ill, piperacillin/tazobactam, meropenem

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Introduction

Piperacillin-Tazobactam is a penicillin and β -lactamase inhibitor combination drug that is widely prescribed in the hospital or critical care setting as first line empirical therapy for nosocomial infections. It is used in the treatment of moderate to severe nosocomial infections including hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), ventilator-associated pneumonia (VAP), community-acquired pneumonia (CAP) with risk factors for *Pseudomonas aeruginosa*, catheter related blood stream infection, complicated skin and soft tissue infections including diabetic foot and necrotizing fasciitis, complicated urinary tract infections, complicated intra-abdominal infection, neutropenic fever, and severe sepsis as well as septic shock (1).

Meropenem is a broad-spectrum antibiotic of the carbapenem family, indicated as the empirical therapy prior to the identification of causative organisms or for diseases caused by single or multiple susceptible bacteria with a broad range of serious infections such as complicated intra-abdominal infection, complicated skin and skin structure infection, nosocomial pneumonia, septicaemia, febrile neutropenia and

for the treatment of severe CAP. Meropenem has a broad spectrum of in vitro activity against Gram-positive and Gram-negative pathogens, including extended-spectrum β-lactamase (ESBL) producing bacteria (2).

Previous studies showed that the combination of Tazobactam and Piperacillin was identified as a cause of delayed renal recovery in critically ill patients. This nephrotoxicity was not observed with the other β -lactam antibiotics (3). In a study conducted by Choudhury *et al.* (4), the combination was only known to increase the level of serum creatinine due to a reduction in tubular creatinine secretion, caused by inhibition of the organic anion transporter. However, in other studies done by Navalkele *et al.* (5) and Hammond *et al.* (6), the combination of Vancomycin and Piperacillin/Tazobactam showed increased risk of acute kidney injury (AKI). A recent series of articles suggested that the combination of Vancomycin and Piperacillin/Tazobactam was synergistically nephrotoxic (7-11). When compared to Meropenem, patients treated with Piperacillin/Tazobactam exhibited delayed improvement in their creatinine during antibiotic therapy (3).

Studies have shown that the use of extended infusion of Piperacillin/Tazobactam did not seem to reduce the risk of AKI compared to standard infusions (12). The two most commonly proposed mechanisms for Piperacillin/Tazobactam-induced AKI were acute interstitial nephritis (AIN) or toxic effects on the renal tubule (13-19). Renal insufficiency from drug-induced AIN usually occurs between three to five days and several weeks from the beginning of the therapy and typically resolves upon discontinuation of the therapy. However, some patients may progress to develop chronic renal failure (20). In a recent study, Piperacillin/Tazobactam had been implicated in causing AIN in at least three case reports (14-16). Furthermore, Piperacillin had been shown to competitively inhibit the organic anion transport system, in a fashion similar to probenecid where it causes the increase in serum creatinine level (21-22)

Many studies were proposing the possibilities of Piperacillin/Tazobactam inducing AKI. There were three intensive care unit (ICU) studies reporting a high rate of AKI with Vancomycin + Piperacillin/Tazobactam (21.2-40.5%) (7, 23-24). Another two of the ICU studies showed a significantly higher rate in the combo group of Piperacillin/Tazobactam and Vancomycin compared with Vancomycin alone (25-26). However, no significant difference was found in the incidence of AKI development or other outcomes between the groups (6) and no studies were showing that Piperacillin/Tazobactam alone increases the risk of AKI.

The high incidence of AKI was reported in combination therapy with Vancomycin and Piperacillin/Tazobactam and to date there was limited study of incidence of AKI in patients treated with Piperacillin/Tazobactam alone. Therefore, this study was designed to compare the occurrence of AKI development or delayed renal recovery during therapy or after completion of therapy in adult critically ill patients who received Piperacillin/Tazobactam or Meropenem.

Method

This study was designed as a retrospective observational study. Patients that were eligible for this study were from the ICU of Hospital Sultanah Aminah, Johor Bahru who fulfilled the inclusion criteria during the study period from 1 January 2015 – 30 June 2018. In this study, the inclusion criteria were all adult patients over the age of 18 years in ICU who were treated with intravenous Piperacillin/Tazobactam or Meropenem, patients who stayed in the ICU for at least 24 hours, diagnosed with severe sepsis or septic shock with or without AKI, and patients who received a minimum of 72 hours of Piperacillin/Tazobactam or Meropenem therapy. Meanwhile, patients who had AKI on chronic kidney disease (CKD) and end-stage renal failure (ESRF), sepsis with meningitis and those who received the studied antibiotics other than via the intravenous route of administration were excluded. The Piperacillin/Tazobactam and Meropenem were supplied by the inpatient pharmacy of the hospital.

The sample size was calculated using Power and Sample Size Calculation software version 3.0.43. (Vanderbilt University, Nashville, TN, USA). Allowing for a 10% dropout, a final sample size of 170 per group will be used.

Patients who were prescribed with Piperacillin/Tazobactam or Meropenem were identified by screening the Pharmacotherapy Review Forms (CP2 form). The CP2 is a form used by pharmacists in the Ministry of Health Malaysia (MOH) to document the findings and interventions related to pharmaceutical care issues of warded patients. Patients prescribed with Piperacillin/Tazobactam or Meropenem were registered in a patient's master list. Using the master list, the inclusion and exclusion criteria were reviewed and qualified patients were assigned a running number based on the antimicrobial use in their treatment

either Piperacillin/Tazobactam or Meropenem. Then, further data was obtained from the CP2 form, patients' case notes and laboratory investigation data from the hospital's IT system (Omega system) using a data Collection Form – PTZ01 Study Form. The patients were followed up until the completion or discontinuation of Piperacillin/Tazobactam or Meropenem antibiotic therapy, patient was transferred out from ICU or patient's death.

Comparisons were made between the two groups using Students t-test (for normally distributed continuous data) and Mann Whitney U test (for non-normally distributed continuous data). Pearson Chi-Square test was used to test categorical variables. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) version 24. A two-sided P value of 0.05 and less was considered to be statistically significant.

Results

Clinical Characteristics of the Cohort

A total of 522 patients that were eligible for the study were screened. Of these patients, 290 were excluded. Thus, only 232 patients were included in the study, with 120 patients in the Piperacillin/Tazobactam group and 112 patients in the Meropenem group (Figure 1).

Table 1 summarised the demographic and clinical characteristics of Piperacillin/Tazobactam and Meropenem groups. The Piperacillin/Tazobactam group had a statistically significant shorter mean duration of antibiotic treatment and ICU stay (5 (standard deviation (SD) 2.5) days, and 9.52 (SD 5.9) days, respectively) than the Meropenem group (7 (SD 3.7) days, and 14.62 (SD 9.2) days, respectively). Meanwhile, a significantly higher proportion of patients in the Piperacillin/Tazobactam group was given the antibiotic empirically as opposed to the Meropenem group (85.8% versus (vs) 61.6%; $p<0.05$). Less number of patients in Piperacillin/Tazobactam group showed growth of microorganism in the culture and sensitivity test when compared to the Meropenem group (15% vs 43.8%, $p<0.05$). Three cases (2.5%) of ESBL organisms were identified in the Piperacillin/Tazobactam group compared to 42 cases (37.5%) in Meropenem group. These organisms were categorised as resistant organisms in Table 1.

Occurrence of AKI

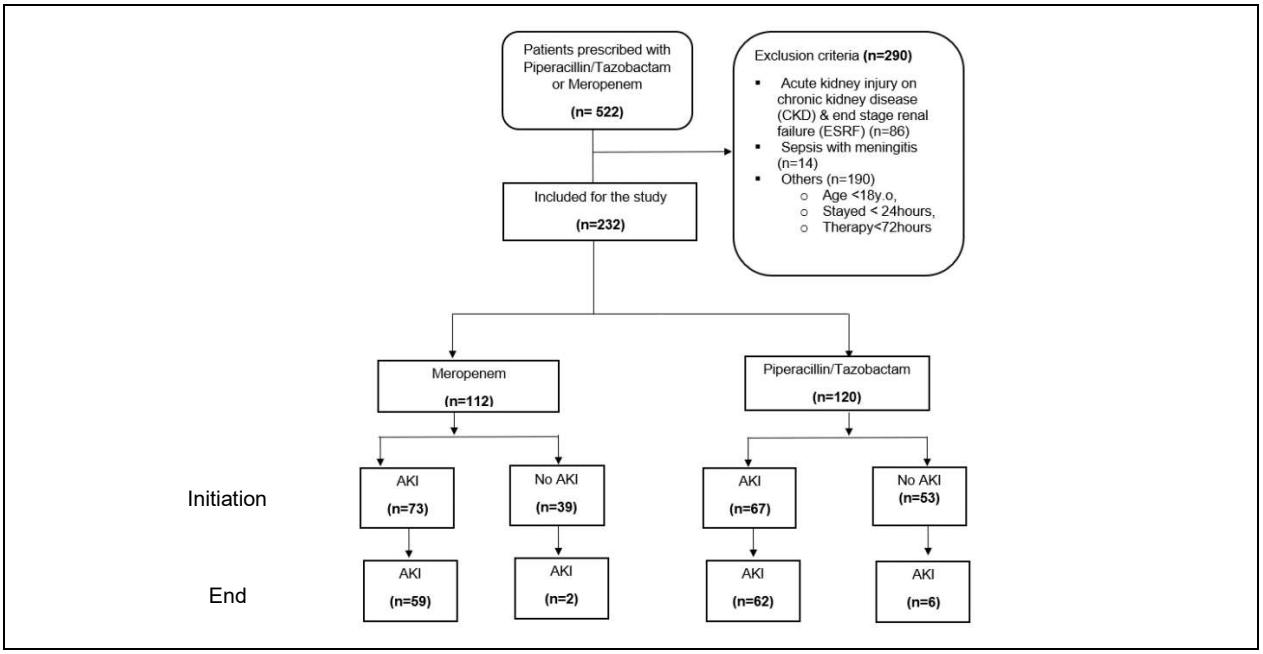
The difference between the number of patients presented with AKI during the initiation of antibiotics in patients receiving Piperacillin/Tazobactam and Meropenem was not statistically significant ($p=0.146$) as reported in Table 2. Similarly, during the last day of follow up, no statistically significant difference was found between the two groups ($p=0.7$).

Renal recovery

This study showed that the occurrence of severely impaired renal function was slightly increased in the Piperacillin/Tazobactam group (Table 3) during the last day of follow up (n=41, 34.%) compared to during initiation of antibiotic (n=36,30%). This was the opposite for the Meropenem group in which during initiation, 43.8% (n=49) of the patients had severely impaired renal function but it decreased to 36.6% (n=41) on the last day of follow up. Meanwhile, an increase in the number of patients with a normal renal function from initiation to the final day of follow up can be seen in both the groups. In Piperacillin/Tazobactam group, the percentage of patients with normal renal function increased from 38.3% (n=46) to 41.7% (n=50) meanwhile in the Meropenem group, it increased from 33.9% (n=38) to 42.9% (n=48).

To investigate further on renal recovery, the CrCl of all patients in both groups during initiation was compared to the CrCl on the last day of follow-up using paired sample t-test (Table 4). In the Piperacillin/Tazobactam group, no renal function improvement was observed (mean CrCl 66.79 ml/min (SD 63.82) to 72.66 ml/min (SD 66.24), $p=0.149$),. In contrary, the Meropenem group showed a significant improvement in CrCl from initiation to the last day of follow up (mean CrCl 55.16 ml/min (SD 51.14) to 83.01 ml/min (SD 108.48), $p<0.05$).

Figure 1: Schematic presentation of the patient selection process for the Piperacillin/Tazobactam and Meropenem groups



Abbreviation: AKI – acute kidney injury; ESRF – end-stage renal failure

Table 1: Demographic and clinical characteristics of the piperacillin/tazobactam and meropenem groups (n=232)

	Pip/Tazo	Meropenem	P-value*
Number of patients, n	120	112	
Age, years, mean (SD)	53.27 (14.8)	50.07 (16.1)	0.12 ǂ
Weight, kg, mean (SD)	68.69 (17.2)	69.74 (16.3)	0.63 ǂ
BMI, kg/m^2, mean (SD)	26.51 (6.34)	26.37 (5.8)	0.87 ǂ
Number of comorbidities, mean (SD)	1.45 (1.3)	1.25 (1.2)	0.23 ǂ
Duration of treatment, mean (SD)	5 (2.5)	7 (3.7)	<0.05 ǂ
Duration of ICU stayed, mean (SD)	9.52 (5.9)	14.62 (9.2)	<0.05 ǂ
Discipline, n (%)			
Medical	77 (64.2%)	61 (54.5%)	
Surgical	34 (28.3%)	47 (42%)	0.06 ǂ
Others	9 (7.5%)	4 (3.6%)	
Site of Infection, n (%)			
Abdomen	23 (19.2%)	16 (14.3%)	
Urinary Tract	7 (5.8%)	3 (2.7%)	
Respiratory	47 (39.2%)	29 (25.9%)	0.02 ǂ
Blood	29 (24.2%)	51 (45.5%)	
Skin & Soft Tissue	5 (4.2%)	8 (7.1%)	
Unknown	8 (6.7%)	4 (3.6%)	
Indication of therapy, n (%)			
Empirical	103 (85.8%)	69 (61.6%)	<0.05 ǂ
Targeted	17 (14.2%)	43 (38.4%)	
Type of Microorganism, n (%)			
No organism	102 (85%)	63 (56.3%)	
Sensitive organism	15 (12.5%)	7 (6.3%)	<0.05 ǂ
Resistant organism	3 (2.5%)	42 (37.5%)	
Patient outcome, n (%)			
Alive	106 (88.3%)	91 (81.3%)	0.13 ǂ
Death	14 (11.7%)	21 (18.8%)	

Abbreviation: Pip/Tazo – piperacillin/tazobactam; SD – standard deviation
Note: ǂ - Independent t-test; ǂ – Pearson Chi Square test

Table 2: Occurrence of AKI among the study population during the initiation of antibiotic treatment and last day of follow up (n=232)

	Initial			Last Day		
	Pip/Tazo	Meropenem	P-value	Pip/Tazo	Meropenem	P-value ǂ
AKI	67(55.8%)	73(65.2%)	0.146	68(56.7%)	61(54.5%)	0.7
Normal renal function	53(44.2%)	39(34.8%)		52(43.3%)	51(45.5%)	

Abbreviation: AKI – acute kidney injury; Pip/Tazo – piperacillin/tazobactam
Note: ǂ – Pearson Chi Square test

Table 3: Renal function of the study population during the initiation of antibiotic treatment and last day of follow up (n=232)

	Pip/Tazo		Meropenem	
	Initial	Last Day	Initial	Last Day
Normal renal function (CrCl: >60 ml/min)	46(38.3%)	50(41.7%)	38(33.9%)	48(42.9%)
Moderately-severely impaired (CrCl: ≤60 ml/min)	38(31.7%)	29(24.2%)	25(22.3%)	23(20.5%)
Severely impaired (CrCl ≤30 ml/min)	36(30%)	41(34.2%)	49(43.8%)	41(36.6%)

Abbreviation: Pip/Tazo – piperacillin/tazobactam; CrCl – creatinine clearance (ml/min)
Note: CrCl was assessed using the Cockcroft and Gault method (28)

Table 4: Recovery of renal function in Piperacillin/Tazobactam and Meropenem groups (n=232)

	Initiation, mean CrCl (SD)	Last day, mean CrCl (SD)	Mean difference in CrCl (SD)	95% confidence interval	P-value *
Pip/Tazo	66.79 (63.82)	72.66 (66.24)	-5.87 (44.21)	-13.86, 2.12	0.149
Meropenem	55.16 (51.14)	83.01(108.48)	-27.85 (81.00)	-43.01, -12.69	p<0.05

Abbreviation: Pip/Tazo – piperacillin/tazobactam; CrCl – creatinine clearance; SD – standard deviation
Note: * - dependent t-test

Discussion

Piperacillin/Tazobactam was widely prescribed in the hospital or ICU setting as first line empirical therapy for nosocomial infections. The recent findings showed that the usage of Piperacillin/Tazobactam in combination with Vancomycin may predispose patients to the increased risk of AKI. This study was caried out to compare AKI development or delayed renal recovery during the therapy or after the completion of therapy in adult critically ill patients who receive Piperacillin/Tazobactam or Meropenem alone. Meropenem is a carbapenem antibiotic that is also commonly used as empirical therapy for nosocomial infections for the patients that had been exposed to another broad-spectrum antibiotic or as targeted therapy. Therefore, Meropenem was chosen as the comparator in this study.

When comparing the two groups, Meropenem was given for a longer duration and the patients in the Meropenem group were associated with a longer ICU stay. This might be because a larger proportion of patients in the Meropenem group (38.4%) was indicated as targeted therapy as compared to Piperacillin/Tazobactam (14.2%).

Our study compared the occurrence of AKI in patients treated with Piperacillin/Tazobactam and Meropenem in the ICU. The occurrence of AKI was found to be comparable between the two groups, but the study by Kadomura *et al.* (28) in non-ICU patients found that the incidence of AKI in patients treated with Piperacillin/Tazobactam (8.6%) alone was significantly higher than that in patients treated with Cefepime (0.9%). Cefepime is an antibiotic from the fourth generation of cephalosporins group. As compared to Meropenem, Cefepime does not provide coverage against anaerobic infection thus it was not

favoured as the first line empirical antibiotic in ICU. As for targeted treatment, Cefepime was also not favoured in view of the resistance pattern caused by ESBL organism. Therefore, the low usage of Cefepime has become the limitation to be used as comparator for this study. Alternatively, Meropenem had been used as comparator by other studies (6).

The incidence of AKI in patients treated with Vancomycin in combination either with Piperacillin or Cefepime was alarming. Hammond *et al.* (7) found that there were no significant differences in the incidence of AKI development between Vancomycin with Piperacillin/Tazobactam and Vancomycin with Cefepime combination groups in critically ill patients. A meta-analysis by Hammond *et al.* (6) found that concomitant use of Vancomycin and Piperacillin/Tazobactam appeared to be associated with a greater incidence of AKI compared to Vancomycin without Piperacillin/Tazobactam. However, this relationship did not exist in studies with at least 50% of patients receiving care in an ICU setting. In both mentioned studies, Vancomycin was given concomitantly with the studied drugs. While Vancomycin has long been associated with AKI, assessment of the impact of Vancomycin trough on incidence of AKI by Navalkele *et al.* (5) found that a discordance in the impact of Vancomycin troughs on toxicity in patients receiving Vancomycin with Piperacillin/Tazobactam compared to those receiving Vancomycin with Cefepime combination. Therefore, incidence of AKI in patients receiving Vancomycin with Piperacillin/Tazobactam was not associated with Vancomycin trough levels.

Meanwhile, in a study by Gomes *et al*. (30), it was found that the incidence of AKI was significantly higher in the Piperacillin/Tazobactam and Vancomycin group (34.8%) compared with the Cefepime-Vancomycin group (12.5%). However, these different findings in non-ICU setting may not be generalizable, as the risk of AKI in critically ill patients may also be increased by various factors such as dynamic volume status, presence of sepsis and its associated inflammation, endothelial dysfunction, adaptive cellular responses to injury, coagulation disturbances, and use of nephrotoxic medications like vasoactive agents, antibiotics, and contrast media (7). The critically ill population also has an increased baseline risk of AKI (31).

Our study also found that renal recovery in the Piperacillin/Tazobactam group was delayed when compared to the Meropenem group. This observation supports the finding by Jensen *et al.* (3), where Piperacillin/Tazobactam was identified as a cause of delayed renal recovery in critically ill patients. In the study, renal recovery was 1.0 ml/min/1.73 m^2/24 h during exposure to Piperacillin/Tazobactam as compared to Meropenem recovering at higher rate of 2.9 ml/min/1.73 m^2/24 h. The mechanism of delayed renal recovery may be the competitive inhibition of renal tubular secretion (3). Meanwhile, Piperacillin had also been shown to competitively inhibit the organic anion transport system, in a fashion similar to Probenecid (21-22). Therefore, this “pseudo-nephrotoxicity” that delays in creatinine reduction may not reflect a true reduction in renal function or actual renal damage.

This study had several limitations. In this study, we used CrCl as the measurement of renal function. Although the changes in CrCl reflect the changes in renal function, CrCl is not the most accurate measure of renal function. It was still used in this study, however, since it has been validated and is closely related to the outcome of these studies. The design of this study utilised retrospective data, thus the accurate documentation had to be assumed. Other than that, the diagnosis of AKI was made based on the recorded creatinine level and diagnosis. The confounding factors that might increase the risk of AKI such as underlying conditions, concomitant use of other nephrotoxic agents or antibiotics were not analyzed. Furthermore, the severity of the patients was not measured in this study and patients were only classified as AKI or non-AKI. Other than that, the shorter ICU stay in the Piperacillin/Tazobactam group comparing to the Meropenem group might contribute to the current finding as there were less time for renal recovery in Piperacillin/Tazobactam due to shorter follow-up period.

Conclusion

The occurrence of AKI in critical care patients receiving Piperacillin/Tazobactam was comparable to those receiving Meropenem, but the renal recovery in the Piperacillin/Tazobactam group was delayed. This study suggested that Piperacillin/Tazobactam does not increase the incidence of AKI in ICU patients but it could delay their renal improvement. These findings may not be generalizable to the whole critically ill population, and thus bigger studies at the national level are recommended.

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Conflict of Interest Statement
No external funding was received and the authors declared no conflict of interest.

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