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Acute kidney injury associated with piperacillin-tazobactam versus other antibiotics combined with vancomycin in critically ill patients: A retrospective cohort study

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ABSTRACT

Introduction: Evidence of acute kidney injury (AKI) induced by piperacillin-tazobactam (Piptazo) versus other broad-spectrum antibiotics (BSA) combined with vancomycin has been established in the literature. However, there is limited evidence regarding these combinations among critically ill patients. This study assessed the risk of nephrotoxicity of Piptazo versus other BSA as an add-on to vancomycin among patients admitted to an intensive care unit (ICU).

Methods: We have reviewed patients' charts retrospectively to investigate AKI incidence among ICU patients receiving Piptazo versus other BSA as an add-on to vancomycin. Furthermore, we have assessed the duration of AKI and ICU stay, as well as the association between patients' criteria and risk of AKI using logistic regression analyses.

Results: A total of 79 patients were included, 50 patients received the Piptazo combination while 29 patients received other BSA combinations. Almost 52 % of the patients in the Piptazo group developed AKI while only 37.9 % of those in the BSA group did, yet the difference was not statistically significant ($p = 0.22$). On the other hand, the risk of AKI was highly associated with vancomycin trough concentration above 20 mcg/mL, nephrotoxic medications, and African descent (OR 7.1, 95 %CI 1.96–25.84, OR 3.94, 95 %CI 1.27–12.2, OR 3.53, 95 %CI 1.1–11.27, respectively).

Conclusion: Although the difference in AKI risk was not statistically significant between Piptazo versus BSA groups, the elevated trough concentration of vancomycin and the concomitant use of nephrotoxic medications, were found to increase the risk of AKI, independently of the combined antibiotics used.

1. Introduction

Acute kidney injury (AKI) is a major public health problem affecting millions worldwide. It is associated with increased mortality rate, length of hospital stay, and cost of healthcare (Chertow et al., 2005). It was estimated that AKI affected 21.6% of hospitalized adults (Susantitaphong et al., 2013), and this risk is even higher at 30–60% for patients admitted to intensive care units (ICUs) (Singbartl & Kellum, 2012). Additionally, several health-related conditions and exposure to nephrotoxic materials have been recognized to increase the risk of AKI, and nephrotoxic medications are one example of these nephrotoxins (Singbartl & Kellum, 2012). The risk of nephrotoxicity associated with vancomycin has been widely studied and documented in the literature. Larger doses, frequent doses and longer duration of vancomycin therapy have significantly contributed to the incidence of AKI (Bamgbola, 2016).

Combining vancomycin and piperacillin-tazobactam (Piptazo) is considered one of the most commonly used empiric antibiotics (Magill et al., 2014). In 2011, two studies conducted by Hellwig et al. and Min

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et al. raised concerns about the high risk of AKI associated with vancomycin-Piptazo combination versus vancomycin monotherapy (Hellwig, 2011; Min, 2011). These concerns were confirmed in 2014 when Meaney et al. and Burgess et al. found increased risks of AKI when vancomycin and Piptazo combined (Burgess & Drew, 2014; Meaney et al., 2014). However, the need for empiric antibiotics that have a broad-spectrum activity with Methicillin-resistant Staphylococcus aureus (MRSA) and pseudomonal coverage, necessitates combining vancomycin with other broad-spectrum antibiotics (BSA) such as aztreonam, ceftazidime, meropenem, ceftriaxone, imipenem, or cefepime. Nevertheless, conflicting results were published regarding the risk of AKI due to such combinations (Al Yami, 2017; Buckley et al., 2018; Gomes et al., 2014; Hammond et al., 2016; Jeon et al., 2017; Moenster et al., 2014; Mullins et al., 2018; Navalkele et al., 2017; Peyko et al., 2017). However, the majority of these studies have been conducted in non-critically ill patients. Lastly, a recent *meta*-analysis that included general hospitalized and critically ill patients reported that 22% of adult patients who received vancomycin-Piptazo combination developed AKI compared to 13% of patients who received vancomycin alone, vancomycin and cefepime combination, or carbapenem or Piptazo alone (OR 3.12; 95 %CI 2.04–4.78) (Luther et al., 2018).

Moreover, multiple health conditions and nephrotoxic medications were previously recognized as risk factors for AKI. These risk factors include diabetes mellitus, contrast media, malignancy, advanced age, hyper- or hypotension, sepsis, low albumin level and volume depletion (Elyasi et al., 2012). The nephrotoxic medications that were recognized to increase the risk for AKI include aminoglycosides, amphotericin B, foscarnet, cidofovir, loop diuretics, ACEIs, cyclosporine, sirolimus, zonisamide, topiramate, and lithium (Goldstein, 2016).

There is limited data on the incidence of AKI among ICU patients receiving empirical antimicrobial therapy with vancomycin-Piptazo combination. Therefore, the present study was conducted to assess primarily the incidence of AKI in patients receiving vancomycin-Piptazo combination compared to vancomycin with other BSA. The secondary objective of the study was to evaluate the association between the occurrence of AKI and other covariates to determine patients' criteria that were associated with an increased risk of AKI.

2. Methods

2.1. Study design and subjects

We have reviewed patients' charts retrospectively to investigate AKI incidence among ICU patients receiving Piptazo versus BSA as an add-on to vancomycin in a community teaching hospital located in Columbus city, state of Gerorgia, USA. Patients were included if they were at least 18 years old, received a combination of vancomycin and Piptazo or other BSAs such as aztreonam, ceftazidime, meropenem, ceftriaxone, imipenem, or cefepime, for at least 48 hours of therapy during an ICU stay between July 2017 and June 2018, and had a baseline measurement of serum creatinine upon hospital admission. Patients were excluded if they had renal replacement therapy at the start of antibiotic therapy, structural kidney diseases, an estimated creatinine clearance using the Cockcroft-Gault equation of less than 30 ml/min at the initiation of vancomycin combination therapy, febrile neutropenia, or patients with cancer, because those are considered as high metabolizer and that could affect the clearance of vancomycin. Patients were also excluded if AKI occurred prior to treatment, within 48 hours of treatment initiation, or more than 7 days after treatment completion.

2.2. Study outcomes and data collection

The primary outcome of the study was the occurrence of AKI during antimicrobials combination therapy. The AKI was defined based on the Acute Kidney Injury Network (AKIN) criteria; namely, an increase in SCr by 0.3 mg/dl, or oliguria, which is defined as a reduction in urine output to less than 0.5 mg/kg/hour for at least six hours (Mehta et al., 2007). The secondary outcomes were the association between the occurrence of AKI and other covariates; which include age, gender, race, comorbidities, antibiotic indications, concomitant use of other nephrotoxic medications, vancomycin trough concentration, prolonged use of vancomycin, the duration of AKI (defined as time in days between the onset and resolution of AKI), and length of ICU stay (defined as time in days between the admission to and discharge from the ICU). Data were collected retrospectively from the patients' files and organized in an Excel sheet and random patient identification number was used to replace patients' identifiers. The study was approved by the Institutional Review Board (IRB) at Mercer University, State of Georgia, USA.

2.3. Statistical analysis

Descriptive and inferential statistics were used to analyze the outcomes, and the choice between these statistics depends upon the type of variables. Patients' characteristics were reported using mean ± SD and/or proportions, and *t*-test and x^2 test were used to analyze continuous and categorical data, respectively. Multivariate logistic regression was used to analyze the association between the occurrence of AKI and other covariates. Based on the findings from Gomes et al. study in 2014, to detect a 24 % increase in the rate of AKI with vancomycin-Piptazo combination compared to vancomycin with other BSA using an α level of 0.05 and to achieve a power of 80 %, 50 patients in each group were needed (Gomes et al., 2014). All statistical analyses were completed on IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

3. Results

A total of 340 patient charts were evaluated, 261 patients were excluded and 79 patients from the ICU were included in the study, 50 patients in the vancomycin-Piptazo group and 29 patients in the vancomycin-BSA group, which include 9 patients on aztreonam, 8 patients on ceftazidime, 6 patients on meropenem, 3 patients on

Table 1
Baseline characteristics.

Patients Characteristics	Vancomycin + Piptazo (50 patients)	Vancomycin + other BSA (29 patients)	*p*-value
Age (mean, SD)	64 (±13.4)	60 (±18.2)	0.373
Gender, Male (%)	30 (60)	17 (59)	0.904
Race (%)	23	12	0.690
Black	(46)24	(41)17	
All others	(54)	(59)	
Comorbidities (%)	33	16	
Sepsis	(66)36	(55)17	0.725
Hypo/Hypertension	(72)13	(58)10	0.225
Diabetes	(26)	(34)	0.427
Antibiotic indication (%)	33	16	0.173
Sepsis	(66)8	(55)4	
Hospital acquired	(16)3	(14)6	
pneumonia	(6)5	(21)3	
Empiric	(10)1	(10)	
Community acquired	(2)	0	
pneumonia			
Intra-abdominal			
infection			
Use of other nephrotoxic medications (%)	18 (36)	15 (51)	0.175
Baseline SCr mg/dl (mean, SD)	1.17 (±0.3)	1.14 (±0.3)	0.865
Vancomycin conc. ≥ 20 mcg/mL (%)	23 (46)	10 (34.5)	0.315

Abbreviations: BSA: broad-spectrum antibiotics, Piptazo: Piperacillin-tazobactam, SD: standard deviation, SCr: Serum creatinine, conc.: concentration.

ceftriaxone, and 1 patient on imipenem, gentamicin, or cefepime. Baseline characteristics were similar between the two groups, See Table 1. The population was 60 to 64 years old on average in the two groups, and about 60 % of them were male. The mean of vancomycin trough concentrations for the Piptazo and BSA groups were 19.6 and 17.4 mcg/mL, respectively. The proportion of patients with vancomycin trough concentration ≥ 20 mcg/mL was 46 % in the Piptazo group compared to 34.5 % in the other BSA group. Sepsis was the most common indication for the use of vancomycin combinations. There was no statistically significant difference between the two groups in terms of patients' gender, race, the proportion of patients with comorbidities, or the concomitant use of nephrotoxic medications. The patients' baseline characteristics are presented in Table 1.

Twenty-six patients (52 %) in the Piptazo group and 11 patients (37.9 %) in the BSA group developed AKI. However, this difference was not statistically significant ($p = 0.22$). Moreover, the differences in the duration of AKI and length of ICU stay between the two groups were not statistically significant ($p = 0.56$) and ($p = 0.18$), respectively. The primary and secondary outcomes for the two groups are presented in Table 2.

In the multivariate logistic regression, vancomycin trough concentration ≥ 20 mcg/mL (OR 7.1, 95 %CI 1.96–25.84), concomitant use of nephrotoxic medications (OR 3.94, 95 %CI 1.27–12.2), and the Black race (OR 3.53, 95 %CI 1.1–11.27) were associated with an increased risk of developing an AKI in critically ill patients receiving vancomycin in either combinations. Moreover, the odds of developing AKI were dependent on the vancomycin trough concentration (OR 1.19, 95 %CI 1.08–1.32). Whereas age, gender, type of antimicrobial combinations used, length of ICU stay, and comorbidities were not identified as independent risk factors for AKI in these patients. The findings from the multivariate logistic regression are presented in Table 3.

4. Discussion

Vancomycin has long been known to increase the risk of development of AKI and recent studies have shown that this risk may be further increased with the addition of Piptazo (Bamgbola, 2016; Burgess & Drew, 2014; Elyasi et al., 2012). Burgess and Drew (2014) found that 16.3 % of patients on the vancomycin-Piptazo combination developed AKI compared to 8.1 % in the vancomycin alone group (Burgess & Drew, 2014). A *meta*-analysis conducted by Hammond et al. (2017) found that 11 % to 48.8 % of patients on vancomycin-Piptazo combination developed an AKI, and they had about three times the odds of developing AKI (OR 3.12, 95 % CI 2.04–4.78) compared to patients who were using vancomycin in combination with any other beta-lactam therapy, where only 7.7 % to 28.8 % of patients on the later combination had an AKI (Hammond et al., 2017). Robertson et al. (2018) found that there was a higher incidence of AKI in the vancomycin-Piptazo combination when compared to the vancomycin-meropenem combination (16.5 % vs. 3.6 %; $p = 0.009$) (Robertson et al., 2018). A large *meta*-analysis conducted by Bellos and colleagues (2020) that included more than 56 thousand participants revealed that a combination of vancomycin-Piptazo was associated with high AKI compared to its parallel use with cefepime or meropenem (Bellos et al., 2020). Furthermore, in 2021, a large review summarized the current literature on vancomycin-Piptazo combination and nephrotoxicity compared to vancomycin alone or other beta-lactam antibiotics, it concluded that this is becoming a major medication safety topic that require close monitoring (Blair et al., 2021).

In the present study, AKI affected about one-half of the patients in the vancomycin-Piptazo group compared to around one-third of the patients in the vancomycin-BSA group. Nevertheless, this difference between the two groups may not have reached the level of statistical significance because of the small sample size for the study (52 % vs. 37 %; $p = 0.22$). Similarly, Al Yami (2017) did not find any statistically significant difference in the incidence of AKI when the use of the vancomycin-Piptazo combination was compared to the vancomycin-meropenem combination (7.41 % vs. 5.33 %, $p = 0.4$) in the general patient population (Al Yami, 2017). Likewise, Hammond et al. (2016) did not find any significant difference in the incidence of AKI when they compared the vancomycin-Piptazo combination to the vancomycin-cefepime combination (32.7 % vs. 28.8 %, $p = 0.64$) in the critically ill patients (Hammond et al., 2016). Moreover, the study did not find any difference between the groups in terms of AKI duration or length of ICU stay, which is consistent with another study (Gomes et al., 2014).

The current study found that the vancomycin concentration ≥ 20 mcg/mL and the use of other nephrotoxic medications were independent risk factors for developing AKI in ICU patients receiving vancomycin in either combination. Similarly, other studies found that vancomycin concentration ≥ 20 mcg/mL and the use of other nephrotoxic medications were independent risk factors for AKI (Burgess & Drew, 2014; Rutter et al., 2017).

The findings from the current study should be interpreted considering the following limitations. Although patients' profiles for the 340 patients who were admitted to the ICU were reviewed, due to the inclusion and exclusion criteria we were only able to include 79 patients. Time limitation plays a major role in including more patients. The primary endpoint did not meet the predetermined power due to the small sample size, which may have impacted the ability to demonstrate statistical significance. Data were retrospectively extracted; therefore, the results are only as good as the data that were documented in the

Table 2
The primary and secondary outcomes.

Outcomes	Vancomycin + Pipatzo (50 patients)	Vancomycin + other BSA (29 patients)	*p*-value
Primary outcome			
AKI	26 (52%)	11 (37.9%)	0.22
Secondary outcome			
AKI duration	4 ±5	3 ±6	0.56
(days)	15.8 ±12.9	12.5 ±9.2	0.18
ICU LOS (days)			

Abbreviations: BSA: broad-spectrum antibiotics, Piptazo: Piperacillin-tazobactam, AKI: Acute kidney injury, ICU LOS: Intensive care unit length of stay, continuous data are reported as mean ± SD.

Table 3
Independent risk factors analysis from the multivariate logistic regression.

Risk factors	Odds Ratio (OR)	95% CI
Age	0.99	0.95-1.03
Gender		
Male	Reference	
Female	0.77	0.23-2.58
Race		
All other races	Reference	
Black	**3.53**	**1.1-11.27**
Antimicrobial combination with vancomycin	Reference	
Other broad-spectrum antibiotics (BSA)	2.3	0.67-7.93
Piperacillin-tazobactam (Piptazo)		
Comorbidities		
Patients without comorbidities	Reference	
Patients with comorbidities	0.99	0.12-8.02
Use of other nephrotoxic medicine		
No	Reference	
Yes	**3.94**	**1.27-12.2**
Vancomycin conc. ≥20 mcg/mL		
No	Reference	
Yes	**7.1**	**1.96-25.84**
Vancomycin conc.	**1.19**	**1.08-1.32**
ICU LOS	0.99	0.95-1.04

Abbreviations: BSA: broad-spectrum antibiotics, Piptazo: Piperacillin-tazobactam, conc.: concentration, ICU LOS: Intensive care unit length of stay.

patients' profiles.

5. Conclusion

The incidence of AKI in critically ill patients who received the vancomycin-Piptazo combination did not significantly differ compared to vancomycin combined with other broad-spectrum antibiotics. The vancomycin trough concentration $\geq$ 20 mcg/mL, patients receiving other nephrotoxic medications, and the black race were independent risk factors that increased the risk of AKI in ICU patients receiving vancomycin in either combination. Finally, large multicenter studies are needed to identify the safest vancomycin combination as empiric therapy and other risk factors for AKI in critically ill patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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