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Comprehensive Study of Vancomycin and Piperacillin/Tazobactam inducedAcute Kidney Injury

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Abstract: Background: In people without any acute disease, acute kidney injury is increasingly shown in primary care and awareness of the condition must be increased between primary health care professionals. **Aim of the Work:** To discuss comparison of the incidence of Vancomycin and Piperacillin/Tazobactam induced Acute Kidney Injury in hospitalized patients, especially critically ill patients with Acute Broncho-Pneumonia. Efficacy of renal replacement therapy will be evaluated. **Patients and Methods:** The prospective research involved 75 adult patients aged 18 years and older admitted to ICU with broncho-pneumonia and normal kidney functions. All patients were divided into 3 groups; the first group composed of 25 patients who received Vancomycin as monotherapy, the second group consisted of 25 patients who received Piperacillin/Tazobactam as monotherapy, and the third group consisted of 25 patients who received combined Vancomycin/Piperacillin. **Results:** regarding incidence of AKI there was only 1 case (4%) of Vanc. group who developed AKI, while there were another 4 cases (16%) of Piptazo. group and 6 cases (24%) of comb V/P group who developed AKI (p=0.100). **Conclusion:**Compared with vancomycin monotherapy and piperacillin / tazobactam monotherapy, there is an increased risk of acute kidney injury correlated with the combination of vancomycin and piperacillin / tazobactam.
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Introduction

Acute kidney injury (**AKI**) is one of the major triggers of morbidity and mortality in critically ill **patients in intensive care units (ICUs), despite** advancements in supportive care measurements. In ICU patients, there are several factors that can affect renal function, such as hypotension and the usage of medicines that cause renal dysfunction [(1)].

In people without any acute disease, acute kidney injury (**AKI**) is increasingly shown in primary care and awareness of the condition must be increased between primary health care professionals [(2)].

In hospitalized patients, acute kidney injury is a frequent occurrence; with related mortality rates of up to 35-50 % have been recorded[(3)].

We can consider acute kidney injury as a syndrome rather than a clinical condition, and the underlying etiology needs to be established in order to provide appropriate care and predictive guidance. History is also a source of information for diagnosis. Early detection of acute kidney injury is significant, as acute kidney injury could be reversed if adequately handled, and the length and severity of acute kidney injury is associated with clinical results. Key investigations include blood, urine and radiological tests. Serum creatinine is commonly utilized for acute kidney injury as a biomarker, and is the key component of the KDIGO criteria [(4)].

We can identify acute kidney injury in various ways; the most recent is that in acute kidney injury, tubular genes and proteins may be rapidly up-regulated as a reply to injury, thereby appearing in the urine. Important new biomarker characteristics can be used as markers of change in GFR, such as serum **C**ystatin C, while others reflect tubular injury, such as urinary **K**idney **I**njury **M**olecule-**1** (**KIM-1**) and **N**eutrophil **G**elatinase-**A**ssociated **L**ipocalin (**NGAL**) as well as **L**iver-type **F**atty **a**cid-**B**inding **P**rotein (**L-FABP**), **I**nter **L**eukin-**18**(**IL-18**), **N-A**cetyl-b-D **G**lucosaminidase (**NAG**), **M**onocyte **C**hemotactic **P**eptide-**1** (**MCP-1**), **Netrin-1**. **NGAL** was most useful (81% specificity, 68% sensitivity at a 104-ng/ml cutoff) in diagnosis and prediction of AKI severity and duration[(5)].

Appropriate treatment of AKI involves management of the underlying etiology, when possible, and use of non-dialytic therapies like; fluids and vasopressors, nutrition and glycemic control, diuretics, vasodilator therapy (dopamine, fenoldopam, and natriuretic peptides), avoiding nephrotoxins, and dialytic therapies [(4)].

In the form of **R**enal **R**eplacement **T**herapy (**RRT**), some patients need supportive care for acute kidney injury. An area of controversy is the best time to begin RRT in acute kidney injury, but this clinical decision is dependent on many variables, involving urea, serum potassium, fluid and acid-base balance, and the existence of other complications [(5)].

Vancomycin is an antibiotic used to treat severe, life-threatening Gram-positive bacterial infections that do not respond to other antibiotics. For the treatment of septicemia and lower respiratory tract, skin, and bone infections caused by Gram-positive bacteria, Vancomycin is regarded a last resort drug. [(6)].

The combination antibiotic comprising the extended spectrum penicillin antibiotic piperacillin and the inhibitor of β-lactamase tazobactam is piperacillin / tazobactam. Its primary applications are those in intensive care medicine (pneumonia). The National Institute for Health and Care Excellence recommends piperacillin / tazobactam as a first-line treatment to treat bloodstream infections in patients with neutropenic cancer.[(7)].

Aim of the Work

Our study aims to discuss comparison of the incidence of Vancomycin and Piperacillin/Tazobactam induced Acute Kidney Injury in hospitalized patients, especially those critically ill, with Acute Broncho-Pneumonia. Efficacy of renal replacement therapy will be evaluated.

Patients and Methods

This is prospective research involving adult patients aged 18 years and older who have been accepted to ICU with broncho-pneumonia and normal kidney functions in order to study the incidence of Vancomycin and Piperacillin/Tazobactam induced acute kidney injury in hospitalized patients. This study included 75 patients.

Patients were categorized into 3 groups. The first group consisted of 25 patients who received Vancomycin as monotherapy (Vanc. Group), the second group consisted of 25 patients who received Piperacillin/Tazobactam as monotherapy (Piptazo. Group), and the third group consisted of 25 patients who received combined Vancomycin/Piperacillin (comb V/P Group).

At least one of the two following criteria determines AKI regarding serum creatinine level:

(1) ≥1.5-fold serum creatinine increase from admission baseline.

(2) Increase in serum creatinine ≥0.5 mg/dl from admission baseline.

Criterion **1**is the lowest level of kidney injury identified by the scoring system **RIFLE** (**R**isk, **I**njury, **F**ailure, **L**oss, **E**nd-stage Kidney Disease), used and shown to be correlated with in-hospital mortality. Criterion **2**was suggested as a responsive measure of kidney injury which also makes it possible to detect higher baseline creatinine levels in patients, but still related to duration of stay and mortality.

Study Population:

Inclusion criteria:

All patients ≥18 years of age admitted to ICU with broncho-pneumonia and normal kidney functions.

Exclusion criteria:

Patients with chronic kidney diseases, past history of other chronic diseases like DM, HTN, and IHD and patients who received antibiotics for less than 48 hours will be excluded from the study.

All patients were subject to informed approval and taking of history, involving personal history: age, gender, job and residence, history of chronic diseases: DM, HTN and IHD, history of chronic kidney diseases and drug history.

Clinical examination:

All patients were subjected to thorough clinical examination.

Laboratory analysis:

All patients were subjected to routine laboratory investigations with special emphasis to kidney function tests.

Ethical Considerations:

Informed consent:

All patients have offered written informed consent. In line with the Declaration of Helsinki and the principles of good clinical practice, the research was conducted. The research was accepted by the Ain Shams University Faculty of Medicine's Ethics Committee.

Confidentiality of patient's data:

There were adequate provisions to maintain privacy of participants and confidentiality of the data, and the names of participants were hidden and replaced by code numbers.

We used the results of the research only for scientific purposes and not any other aim.

Measures to minimize risks of the research in the study:

The waste products were discarded according to the infection control policy of Ain Shams University Hospitals. The risk of infection during taking the samples was minimized by using complete aseptic techniques.

Statistical analysis of the data:

Using Microsoft Excel 2013, the data was compiled, revised, and edited into a master table. The data was then revised, encoded and inserted in version 22 of the statistical package for social science (SPSS).

Patient demographic characteristics for continuous variables with normal distribution, median and interquartile range (IQR) were described as mean and standard deviation for continuous variables with

non-normal distribution and as proportions (percentages) for categorical variables.

For normally distributed data, a one-way ANOVA test was used to compare the three population subgroups, followed by a Post Hoc (Tukey) test when significant differences were observed.

For abnormally distributed data, where significant differences were observed, a comparison was made between two of the three population subgroups using the Kruskal-Wallis test, followed by the Post Hoc test. For categorical variables, simple three-group comparisons were conducted using the $\chi 2$ (Chi-square) test.

Using the Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test, the distributions of quantitative variables were tested for normality, and Histogram and QQ plot were also utilized for the for vision test. If normal data distribution is revealed, parametric tests are used. Non-parametric tests were used if the data was abnormally distributed.

• P: The probability/significance value:

P value >0.05 (NS) Not significant.

P value <0.05 *Significant at 0.05 level.

P value <0.01 **Highly Significant at 0.01 Level.

3. Results

Demographic data:

Table 1. Distribution of demographic data among study population.

Parameter		Description
Age:	Mean ± SD	35.46 ± 11.5
(years)	Range	18 – 60
Sex	Male	47 (62.7%)
[No. (%)]	Female	28 (37.3%)
BMI:	Mean ± SD	25.82 ± 4.12
(kg/m^2)	Range	18.5 – 37

Serum Creatinine on Admission:

Admission serum creatinine level showed a median result of 0.8 mg/dL and an interquartile range of (0.7, 1.0) mg/dL with a maximal level of 0.6 mg/dL and a minimal level of 1.2 mg/dL (Table 2).

Table 2. Distribution of serum creatinine level on admission among study population.

Parameter		Description
S. Cr:	Median & IQR	0.8 (0.7&1.0)
(mg/dL)	Range	0.6 – 1.2

Incidence of AKI:

During regular follow up; out of the 75 patients, 11 patients (14.7%) developed AKI during the course of antibiotic treatment, while 64 patients (85.3%) passed their treatment course safely (Table 3).

Table 3. Incidence of AKI among study population.

Parameter		Description
AKI	Yes	11 (14.7%)
[No. (%)]	No	64 (85.3%)

Inferential statistics

Demographic data:

Male patients represented 56% of Vanc. group (14 patients), 64% of Piptazo. group (16 patients) and 68% of comb V/P group (17 patients). As regarding females there were 11 cases (44%) of Vanc. group and another 9 cases (36%) of Piptazo. group, vs. 8 cases (32%) of comb V/P group (p=0.672), (Table 4).

The mean age was 34.6 ± 11.2 years in Vanc. group, and 36.04 ± 12.0 years in Piptazo. group while it was 36.28 ± 11.8 years in comb V/P group (p=0.859), (Table 4).

The mean BMI was 25.7 ± 4.6 kg/m^2 in Vanc. group, and 26.3 ± 3.7 kg/m^2 in Piptazo. group while it was 25.5 ± 4.1 kg/m^2 in comb V/P group (p=0.778), (Table 4).

Table 4. Comparison between the studied groups regarding demographic data.

Parameter		Vanc. (n=25)		Piptazo. (n=25)		Comb V/P (n=25)		Test of sig. *	*P*-Value
		No.	%	No.	%	No.	%		
Sex [No. (%)]	Male	14	56%	16	64%	17	68%	χ^2 = 0.795	0.672
	Female	11	44%	9	36%	8	32%		
Age (years)	Mean ± SD	34.6 ± 11.2		36.04 ± 12.0		36.28 ± 11.8		*F*=0.152	0.859
	Range	18-59		18-60		18-60			
BMI (kg/m^2)	Mean ± SD	25.7 ± 4.6		26.3 ± 3.7		25.5 ± 4.1		*F*=0.252	0.778
	Range	19-37		18.5-32.5		18.5-35.7			

*χ^2: Pearson's Chi square test of association. *F*: One way ANOVA test.

The previous table indicates that,no statistically substantial difference in terms of age, sex and BMI among the three groups studied with P-values > 0.05.

Serum Creatinine on Admission:

The admission serum creatinine level showed a median value of 0.8 mg/dL with an IQR of (0.7, 1.0) mg/dL in Vanc. group, 0.8 (0.7, 0.9) mg/dL in Piptazo. group and 0.8 (0.7, 1.0) mg/dL in comb V/P group (p = 0.863), (Table 5).

Table 5. Comparison between the studied groups regarding admission serum creatinine level.

Parameter		Vanc. (n=25)	Piptazo. (n=25)	Comb V/P (n=25)	Test of sig. *	*P*-Value
S. Cr (kg/m^2)	Median&IQR	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	*H*= 0.296	0.863
	Mean rank	39.36	36.16	38.48		

**H*: Kruskal-Wallis test.

The previous table indicates that, no statistically substantial difference among the three groups studied in the admission serum creatinine level with a P-value > 0.05.

Incidence of AKI:

As regarding incidence of AKI there was only 1 case (4%) of Vanc. group who developed AKI, while there were another 4 cases (16%) of Piptazo. group and 6 cases (24%) of comb V/P group who developed AKI (p=0.100) (Tables 6).

Table 6. Comparison between the studied groups regarding incidence of AKI.

Parameter		Vanc. (n=25)		Piptazo. (n=25)		Comb V/P (n=25)		Test of sig. *	*P*-Value
		No.	%	No.	%	No.	%		
AKI [No. (%)]	Yes	1	4%	4	16%	6	24%	χ^2 = 0.795	0.100
	No	24	96%	21	84%	19	76%		

* χ^2: Pearson's Chi square test of association.

Table 7 indicates that there was an overall statistically insignificant differences among the three groups studied regarding incidence of AKI.

While pair-wise comparison (table 14) reveals statically significant difference as regard to AKI incidence between Vanc. group and comb V/P group (P<0.05). And there was no substantial difference among the group Piptazo. and either the group Vanc. or comb V/P group.

Table 7. Pair-wise comparison between each two of the three studied groups regarding incidence of AKI.

Parameter	Vanc. vs. Piptazo.		Piptazo. vs. Comb V/P		Vanc. vs. Comb V/P	
	χ^2	*P*	χ^2	*P*	χ^2	*P*
AKI	2	0.157	0.5	0.48	4.15	**0.042**

* χ^2: Pearson's Chi square test of association.

4. Discussion

In view of the high prevalence of infections caused by drug-resistant pathogens in hospitalized patients, the use of empirical broad-spectrum antibiotics would be widespread in the near future.

Up to 23 % of hospitalized patients with an associated mortality of 11 % will experience acute kidney injury. AKI rates are elevated in the intensive care unit, with a documented occurrence of up to 66% and a similar rise in ICU mortality. Several drugs are contributing to the development of AKI, including antimicrobials such as Vancomycin and Piperacillin / Tazobactam. In patients receiving daily doses of > 4 gram, vancomycin-associated nephrotoxicity rates can be as high as 34.6 %. In addition to higher doses of vancomycin, the risk indicators for vancomycin-associated nephrotoxicity are multifaceted and involve raised body weight, prolonged period of treatment, history of kidney disease, higher disease severity, hypotension, increased trough concentrations, and concomitant nephrotoxic drugs, including other antimicrobials.[8].

Historically, nephrotoxicity, frequently characterized by acute interstitial nephritis, has been independently related to beta-lactam antibiotics. Literature on the possible synergistic nephrotoxicity correlated with concomitant vancomycin and antipseudomonal beta-lactam (e.g., piperacillin/ tazobactam) therapy has been limited until recently. Considering the commonality of vancomycin and beta-lactam empirical combination therapy, the potential potentiation for nephrotoxic effects of vancomycin is a clinically valuable issue and could represent a modifiable risk factor for nephrotoxicity associated with vancomycin. The aim of this systemic review and meta-analysis was to decide whether concomitant vancomycin and piperacillin / tazobactam are correlated with a higher occurrence of AKI relative to vancomycin with any beta-lactam other than piperacillin / tazobactam or monotherapy.[8].

We found in this prospective study of seriously ill patients that during combination of Vancomycin and Piperacillin / Tazobactam treatment, the chances of AKI were more than five times higher relative to Vancomycin monotherapy.

A prospective research was performed in critically ill patients with acute bronchopneumonia to compare the occurrence and risk factors for AKI in patients receiving combinations of Vancomycin and Piperacillin/Tazobactam against monotherapy with either medication.AKI was described as either: **(1)**Serum creatinine increase ≥0.5 mg/dl OR **(2)** ≥1.5-fold creatinine increase from baseline admission [9].

There are many studies were published from 2014 to 2016 focused on the comparison between the incidence of and risk factors for AKI in patients who receive Vancomycin and Piperacillin/Tazobactam combinations versus monotherapy with either drug in critically ill patients. Each research included similar AKI definitions to ours, and both also demonstrated that AKI was independently correlated with the combination of Vancomycin and Piperacillin/ azobactam compared with Vancomycin monotherapy.

The research by **Burgess et al.** [10] analyzed 191 patients who had undergone Vancomycin medication. A combination of Vancomycin and Piperacillin / Tazobactam was correlated with an AKI odds ratio of 2.48 (p = 0.041) relative to Vancomycin monotherapy in a multivariate analysis.

Theresearch by **Meinelet al.** [11]analyzed 125 patients treated with Vancomycin. Again, relative to Vancomycin monotherapy, the combination of Vancomycin and Piperacillin / Tazobactam was correlated with an AKI odds ratio of 5.36 (95 % CI 1.41-20.5).

The research by **Gomez et al.** [12]analyzed 224 patients who had obtained Vancomycin treatment. The combination of Vancomycin and Piperacillin/ Tazobactam was correlated with an AKI odds ratio of 5.67 (p = 0.006) relative to Vancomycin monotherapy in a multivariate analysis.

The research by **Moenster et al.** [13] analyzed 139 patients who had obtained Vancomycin treatment. The combination of Vancomycin and Piperacillin/ Tazobactam was correlated with an AKI odds ratio of 3.45 (p = 0.06) relative to Vancomycin monotherapy in a multivariable analysis.

The research by **Sutton et al.** [14] analyzed 292 patients who had obtained Vancomycin treatment. The combination of Vancomycin and Piperacillin/ Tazobactam was correlated with an AKI odds ratio of 3.97 (p = 0.002) relative to Vancomycin monotherapy in a multivariate analysis.

The research by **Kim et al.** [15] analyzed 228 patients who had obtained Vancomycin treatment. The combination of Vancomycin and Piperacillin/ Tazobactam was correlated with an AKI odds ratio of 7.14 (p = 0.06) relative to Vancomycin monotherapy in a multivariate analysis.

The research by **Fodero et al.** [16]analyzed 453 patients who had undergone Vancomycin treatment. A combination of Vancomycin and Piperacillin / Tazobactam was correlated with an AKI odds ratio of 3.21 (p = 0.03) relative to Vancomycin monotherapy in a multivariate analysis.

The research by **Hammond et al.** [8] analyzed 122 patients who had undergone Vancomycin treatment. The combination of Vancomycin and Piperacillin / Tazobactam was correlated with an AKI odds ratio of 1.44 (p = 0.06) relative to Vancomycin monotherapy in a multivariate analysis.

The research by **Navalkele et al.** [17] analyzed 558 patients who had undergone Vancomycin treatment. A combination of Vancomycin and Piperacillin/Tazobactam was correlated with an AKI odds ratio of 4.27 (95 %CI 2.7-6.7) relative to Vancomycin monotherapy in a multivariate analysis[8].

Our study provides further proof of this association and provides additional evidence which indicates the same statistically significant AKI odds ratio correlated with combination of Vancomycin and Piperacillin/Tazobactam. In order to assess such risks, a randomized controlled trial would be ideal. At this time, the mechanisms which could underpin AKI during combV / P are not apparent. Beta lactam agents are alleged to cause AKI through interstitial nephritis, particularly penicillin derivatives. [15].

In our study, the overall incidence of Acute Kidney Injury was 14.7%. In 4 % of Vanc. group patients, AKI happened,In the Piptazo group, 16 %of patients and in the combined V / P group, 24 % of patients. In the Vanc and piptazo group, the univariable AKI odds were substantially lower.

Vancomycin was also the most widely used antibiotic from 2004 to 2006 in a study of data available from 22 university teaching hospitals from 2002 to 2006, and use grew by 43 % over the five-year observation period.

The reported incidence of nephrotoxicity correlated with Vancomycin differs by study, primarily affected by the population of patients, risk factors and definitions of the study; there is no full understanding of the mechanism for such toxicity. By glomerular filtration and some vigorous tubular secretion, vancomycin is primarily removed. Oxidative stress, complement mediated inflammation and necrosis of the renal tubule with Vancomycin accumulation was suggested by one posited mechanism. It was thought that the toxicity found in previous studies was due to impurities in the product. Following the initial development of Vancomycin, modern purification methods resulted in reduced nephrotoxicity rates in later research, typically not exceeding 5% [10].

More recently, there has been increased concern about the rapid rise in Vancomycin nephrotoxicity rates.Several risk factors have been established, but less likely to be related to the formulation, include concomitant serious illness, increased length of treatment, higher serum concentrations of Vancomycin (> 15 µg / ml) and total doses of Vancomycin exceeding 4g/day [18].

While the overall incidence of nephrotoxicity (independent of the treatment group) in our sample of 14.7% was similar to that reported in published studies, the incidence of nephrotoxicity was lower than originally posited in patients who did not receive concomitant Piperacillin / Tazobactam.

In our study, no patient obtained a total daily dose of more than 4 g / day of Vancomycin. However, the correlation of a serum Vancomycin steady-state concentration of 15 mg / L or higher with an increased incidence of nephrotoxicity has been observed in accordance with previous studies.

For improved activity against gram-negative and anaerobic pathogens, vancomycin is usually combined with Piperacillin/Tazobactam. Piperacillin/ Tazobactam, like Vancomycin, showed a considerable rise in use. During the same 5-year period, an 84 % rise in Piperacillin/Tazobactam was recorded in the same study of data available earlier cited for Vancomycin.For instance, 397 (27.5%) and 306 (21.2%) of 1446 patients receiving any antibiotic (oral or intravenous) received Vancomycin and Piperacillin / Tazobactam, respectively, during a 2013-point prevalence survey of inpatient antimicrobial prescribing at Duke University Hospital during a 2-week span. Piperacillin / Tazobactam was also obtained concomitantly by a total of 161 (40.6 %) of the 397 patients receiving Vancomycin. [5].

Piperacillin / Tazobactam use was linked with delayed renal recovery in one study of critically ill patients, performed to assess whether increased exposure to broad-spectrum antibiotics resulted in further renal failure in patients in the intensive care unit.When using other b-lactam antibiotics, this nephrotoxicity has not been observed.In a retrospective study of patients in the surgical intensive care unit, the effect of the addition of Piperacillin/ Tazobactam to Vancomycin monotherapy on the occurrence of nephrotoxicity was documented. In this research, a substantial increase in the incidence of acute kidney injury compared to Vancomycin monotherapy was recorded for patients who received combination treatment. In 49.3 % of patients undergoing combination treatment, acute kidney injury was registered, relative to 8.9 % in the monotherapy group (p=0.02).The combination of Piperacillin/Tazobactam and Vancomycin showed an 18.6 % incidence of acute kidney injury relative to 4.9 % with vancomycin monotherapy (p=0.0001) in a similar retrospective report of hospitalized patients aged 18 years or older. These studies are limited in detail, since they have only been published in abstract form [1].

In current research, nephrotoxicity was more in the range of literature reported in the Vancomycin-plus-Piperacillin / Tazobactam group (24%) and 6-fold in patients treated with Vancomycin who did not receive Piperacillin / Tazobactam. The mechanism by which nephrotoxicity associated with Vancomycin is increased by Piperacillin / Tazobactam is unknown.

Mechanisms that may increase the nephrotoxicity potential of another by concomitant administration of Vancomycin-plus-Piperacillin/Tazobactam may include decreased clearance of Vancomycin by Piperacillin/Tazobactam, and may be assumed to result in accumulation of Vancomycin (and thus increased risk of Vancomycin serum concentration-related nephrotoxicity).

Although the concentration of Vancomycin in the combination group tended to be higher, there was a small variation among the groups and the significance of such small variations is uncertain. However, no data supporting any such mechanism with co-occurring Vancomycin plus Piperacillin / Tazobactam are available and further studies are ensured.

Conclusion:

Compared with vancomycin monotherapy and piperacillin / tazobactam monotherapy, there is an increased risk of acute kidney injury correlated with the combination of vancomycin and piperacillin / tazobactam.

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