Comprehensive Study of Vancomycin and Piperacillin/Tazobactam induced Acute Kidney Injury

Thesis

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Amr Hanafy Mahmoud Mohammed

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List of Abbreviations

ADQI	:	Acute Dialysis Quality Initiative
AIN	:	Altered intra-glomerular hemodynamics papillary necrosis
AKI	:	Acute kidney injury
AKIN	:	Acute Kidney Injury Network
ANA	:	Anti-Nuclear Antibody
ANCA	:	Anti-Neutrophil Cytoplasmic Antibody
anti-GBM	:	Anti-Glomerular Basement Membrane antibody
BMD	:	Broth micro dilution
CC3 & 4	:	Complement Component 3 and 4
CI-AKI	:	Contrast Induced AKI
CKD	:	Chronic kidney disease
CLSI	:	Clinical and Laboratory Standards Institute
C_{max}	:	Mean maximum plasma concentrations
FDA	:	Food and Drug Administration
FENa	:	Fractional Excretion of Sodium
GFR	:	Glomerular Filtration Rate
HUS	:	Haemolytic uraemic syndrome
ICUs	:	Intensive care units
IDSA	:	Infectious Diseases Society of America
IL-18	:	InterLeukin-18
KDIGO	:	Kidney Disease Improving Global Outcomes
KIM-1	:	Kidney Injury Molecule-1
LDH	:	Lactate Dehydrogenase
L-FABP	:	Liver-type Fatty acid-Binding Protein
MCP-1	:	Monocyte Chemotactic Peptide-1
MDRD	:	Modification of Diet in Renal Disease

List of Abbreviations (Cont.)

MICs	:	Minimum inhibitory concentrations
MRSA	:	Methicillin- Resistant Staphylococcus Aureus
NAG	:	N-Acetyl-b-D Glucosaminidase
NGAL	:	Neutrophil Gelatinase-Associated Lipocalin
NICE	:	National Institute for Health and Care Excellence
NT-proBNP	:	N-terminal pro-brain natriuretic peptide
piptazo	:	Piperacillin/Tazobactam
RIFLE	:	Risk, Injury, Failure, Loss, End-stage kidney disease
RRT	:	Renal Replacement Therapy
SCr	:	Serum Creatinine
TDM	:	Therapeutic drug monitoring
TTP	:	Thrombotic thrombocytopenic purpura
UO	:	Urine output
vanc	:	Vancomycin

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Introduction

Despite advances in supportive care measurements, acute kidney injury (**AKI**) remains one of the major causes of mortality and morbidity in critically ill patients in intensive care units (**ICUs**). There are many factors in ICU patients that can impair renal function, such as hypotension, and the use of drugs causing renal dysfunction ***(Clec'h et al., 2012).***

Acute kidney injury (**AKI**) is increasingly being seen in primary care in people without any acute illness, and awareness of the condition needs to be raised among primary care health professionals ***(Lewington et al., 2013).***

Acute kidney injury is a commonly encountered event in hospitalized patients, was reported to have associated mortality rates of up to 35-50% ***(Giuliano et al., 2016).***

We can consider acute kidney injury as a syndrome rather than a specific diagnosis, the underlying etiology must be found in order to deliver effective treatment and guide prognosis. The history is often a source of diagnostic information. The early diagnosis of acute kidney injury is vital, as acute kidney injury can be reversible if treated promptly and the duration and severity of acute kidney injury correlates with clinical outcomes. Key investigations

include blood, urine and radiological tests. The serum creatinine is widely used as a biomarker for acute kidney injury, and is the key component of the KDIGO criteria ***(Duthie et al., 2014)***.

We can identify acute kidney injury in various ways; the most recent is that tubular genes and proteins can immediately be upregulated in acute kidney injury as a response-to-injury reaction, appearing thereby 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 the severity and duration of AKI ***(Lameire et al., 2016)***.

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 (***Duthie et al., 2014***).

Some patients require supportive treatment for acute kidney injury in the form of **R**enal **R**eplacement **T**herapy (**RRT**). The optimal time to start RRT in acute kidney injury is an area of controversy but this clinical decision is based upon several factors including serum potassium, urea, fluid and acid-base balance, and the presence of other complications ***(Lameire et al., 2016)***.

Vancomycin is an antibiotic indicated for the treatment of serious, life-threatening infections by Gram-positive bacteria unresponsive to other antibiotics. Vancomycin is considered a last resort medication for the treatment of septicemia and lower respiratory tract, skin, and bone infections caused by Gram-positive bacteria (***Liu Bayer et al., 2011***).

Piperacillin/tazobactam is a combination antibiotic containing the extended spectrum penicillin antibiotic piperacillin and the β-lactamase inhibitor tazobactam. Its main uses are in intensive care medicine (pneumonia). Piperacillin/ tazobactam is recommended by the National Institute for Health and Care Excellence as first line therapy for the treatment of bloodstream infections in neutropenic cancer patients (***Yeung et al., 2012***).

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 critically ill patients with Acute Broncho-Pneumonia.

Chapter 1

Acute Kidney Injury

Recently acute kidney injury is defined as the abrupt and sustained decrease in renal function, resulting in retention of nitrogenous (urea and creatinine) and non-nitrogenous waste products as well as in dysregulation of cellular volume and electrolyte handling. In clinical practice, the diagnosis of AKI relies on a decreased glomerular filtration rate, increased serum creatinine with or without oliguria, described by two principal classifications: The **R**isk, **I**njury, **F**ailure, **L**oss, **E**nd-stage kidney disease (**RIFLE**) and the **A**cute **K**idney **I**njury **N**etwork (**AKIN**) criteria ***(Piper et al., 2014)***.

The definition of AKI has evolved from the Risk, Injury, Failure, Loss, End-stage **(RIFLE)** criteria in 2004 **(Table 1)** to the AKI Network (**AKIN**) classification in 2007 **(Table 2).** Both were merged resulting in the **K**idney **D**isease **I**mproving **G**lobal **O**utcomes **(KDIGO)** classification **(Table 3)** in 2012 ***(Ostermann et al., 2016).***

In May 2002, the **A**cute **D**ialysis **Q**uality **I**nitiative (**ADQI**) group for the study of AKI, composed of nephrologists and intensivists, came together over 2 days in

a conference in Vicenza (Italy), with the purpose of defining AKI. From this conference, the consensual **RIFLE** (**R**isk, **I**njury, **F**ailure, **L**oss of kidney function, and **E**nd-stage kidney disease) classification for AKI definition emerged. The **ADQI** group considered that the ideal AKI definition would have to accomplish the following criteria: easy clinical applicability, sensitivity and specificity, consider baseline Serum Creatinine **(SCr)** variations and also consider the 'acute-on-chronic' phenomenon (which means the occurrence of an acute insult over a chronically injured renal function causing its deterioration). This definition should classify AKI according to its severity (mild versus severe) and its timing of occurrence (precocious versus late AKI).

By fulfilling these criteria, this classification should allow the detection of patients whose kidney function was slightly affected (high sensitivity but low specificity) as well as patients with severe kidney function deterioration (high specificity with diminishing sensitivity) ***(Lopes et al., 2013)***.

The **RIFLE** classification is based on **s**erum **c**reatinine **(SCr)** and urine output **(UO)** determinants, and considers three severity classes of AKI (**R**isk, **I**njury and **F**ailure),

according to the variations in SCr and/or UO, and two outcome classes (**l**oss of kidney function and **E**nd-stage kidney disease). The patient should be classified using the criteria (SCr and/or UO) which leads to the worst classification (maximum RIFLE), for instance, if a patient was in the **R**isk class according to the UO but in the **I**njury class according to SCr variation, then the worst criteria (SCr) should be used for classifying the severity of AKI in this patient. The temporal pattern of the SCr and/or UO variation is also relevant for defining AKI: the deterioration of renal function must be sudden (1–7 days) and sustained (persisting >24 h) ***(Lopes et al., 2013)***.

Table 1. **RIFLE classification**

	Serum creatinine criteria	Urine output criteria
Risk	Increase serum creatinine to ≥1.5 to 2 fold from baseline, or GFR decrease >25%	<0.5 mL/ kg/ h for >6 h
Injury	Increase serum creatinine to >2fold to 3fold from baseline, or GFR decrease >50%	<0.5 mL/kg/h for >12 h
Failure	Increase serum creatinine to >3fold from baseline, or serum creatinine to ≥354 μmol/L with an acute rise of at least 44 μmol/L, or GFR decrease >75%	<0.3 mL kg/ h for 24h or anuria for 12 h
Loss	Complete loss of kidney function for >4 wk	
End-stage kidney disease	End-stage kidney disease >3 months	

(Joannidis et al., 2009)

This definition can easily be applied when the baseline SCr is known; however, in a significant number of patients baseline SCr is unknown; in these cases, if there is no history of **C**hronic **k**idney **d**isease **(CKD)**, baseline SCr should be calculated using the **M**odification of **D**iet in **R**enal **D**isease **(MDRD)** equation, assuming a baseline **G**lomerular **F**iltration **R**ate **(GFR)** of 75mL/min/1.73m2 ***(Lopes et al., 2013).***