# COMPARISON OF EIGHT METHODS FOR ESTIMATION OF CREATININE CLEARANCE IN MALAYSIA PATIENTS WITH UNSTABLE RENAL FUNCTION

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**by**

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## LIST OF ABBREVIATION

| | |
|---|---|
| ABW | Adjusted body weight |
| ACCP | American College of Clinical Pharmacy |
| ACEi | Angiotensin converting enzyme inhibitor |
| AKI | Acute kidney injury |
| AKIN | Acute Kidney Injury Network |
| APACHE II | Acute physiology and chronic health evaluation |
| ARB | Angiotensin II receptor blocker |
| AUC | Area under the curve |
| BUN | Blood urea nitrogen |
| CCU | Coronary care unit |
| CG | Cockcroft-Gault |
| CKD | Chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| $Cl_{Cr}$ | Creatinine clearance |
| COPD | Chronic obstructive pulmonary disease |
| CRF | Case report form |
| CVA | Cerebro-vascular accident |
| CVD | Cardiovascular disease |
| ECG | Electrocardiogram |
| eGFR | Estimated glomerular filtration rate |

| | |
|---|---|
| eHis | Electronic hospital information system |
| GCP | Good clinical practice |
| GFR | Glomerular filtration rate |
| IBW | Ideal body weight |
| ICH | International Conference on Harmonization |
| ICU | Intensive care unit |
| IQR | Inter quartile range |
| J | Jelliffe |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| MDRD | Modification of diet in renal disease |
| mCG | Modified Cockcroft-Gault |
| mGFR | Measured glomerular filtration rate |
| mJelliffe | Modified Jelliffe |
| NMRR | National Medical Research Register |
| SAPS 2 | Simplified acute physiology score 2 |
| SD | Standard deviation |
| SrCr | Serum creatinine |
| TDM | Therapeutic drug monitoring |
| RAAS | Renin angiotensin angiotensinogen system |
| RIFLE | Risk, injury, failure, loss, end-stage |
| UGIB | Upper gastrointestinal bleeding |
| UO | Urine output |

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**PERBANDINGAN LAPAN KAEDAH ANGGARAN KLEARANS KREATININ DALAM KALANGAN PESAKIT MALAYSIA DENGAN FUNGSI RENAL TIDAK STABIL**

## ABSTRAK

Fungsi buah pinggang yang tidak stabil adalah komplikasi yang biasa berlaku pada pesakit di hospital dan dikaitkan dengan kadar kematian yang tinggi. Pesakit dengan sakit tenat biasanya mempunyai fungsi renal yang berfluktuasi dengan kreatinin serum berubah dari hari ke hari. Anggaran kadar klearans kreatinin (Clcr) amat penting dalam praktis klinikal harian terutamanya dalam kalangan pesakit yang mengalami masalah fungsi buah pinggang yang tidak stabil. Kaedah Cockcroft-Gault kekal sebagai kaedah yang paling banyak digunakan untuk menganggarkan fungsi renal seseorang dan untuk membimbing pengubahsuaian dos ubat. Persamaan Cockcroft-Gault berasal dari keadaan di mana kreatinin serum berada dalam keadaan stabil dan ia tidak sesuai untuk pesakit dengan fungsi buah pinggang yang tidak stabil. Kajian ini bertujuan untuk menganalisis perbezaan anggaran kreatinin klearans yang dianggar oleh persamaan Cockcroft & Gault, MDRD, CKD-EPI, Jelliffe, Jelliffe diubahsuai, Chiou, Brater, dan persamaan anggaran empirik (Cockcroft-Gault diubahsuai) dengan kreatinin klearans urin 24 jam (kawalan piawai) pada pesakit tenat dengan fungsi buah pinggang yang tidak stabil dalam kalangan populasi Malaysia. Ini adalah kajian permerhatian prospektif, pelbagai pusat. Sebanyak 43 pesakit dari tiga hospital awam yang terlibat dalam kajian ini. Pada fasa awal fungsi buah pinggang yang tidak stabil, nilai purata kreatinin klearans urin adalah 20.56±18.47 ml/min. Di antara persamaan-persamaan anggaran kreatinin klearans, hanya kaedah

Cockcroft-Gault yang diubahsuai (20.12±17.19 ml/min) menunjukkan perbezaan yang tidak ketara dengan kreatinin klearans urin ( p = 0.741). Analisis sub-set pada 23 pesakit dengan fungsi buah pinggang yang merosot akut dilakukan. Nilai purata kreatinin klearans urin adalah 11.77±6.27 ml/min. Di antara persamaan-persamman anggaran kreatinin klearans, hanya Cockcroft-Gault diubahsuai (12.72±6.01 ml/min) menunjukkan perbezaan yang tidak ketara dengan kreatinin klearans urin (p = 0.843). Analisis sub-set dilakukan pada 20 pesakit dengan fungsi buah pinggang yang bertambah baik secara mendadak. Ia menunjukkan nilai purata kreatinin klearans urin adalah 30.66±22.53 ml/min. Antara persamaan-persamman anggaran kreatinin klearans, kaedah Chiou meremehkan aggaran kreatinin klerans sebanyak hampir 34%, $p < 0.001$. Analisis Bland-Altman dilakukan untuk menentukan persetujuan di antara Clcr oleh lapan kaedah anggaran klearans dengan Clcr urinari sebagai standard. Semasa kemerosotan akut fungsi buah pinggang, hanya kaedah Cockcroft-Gault yang diubahsuai menunjukkan persetujuan dengan kaedah penyukatan kreatinin urin, $p > 0.05$. Sementara itu, semasa penambahbaikan fungsi buah pinggang, kedah Jelliffe, Brater, Cockcroft-Gault yang diubahsuai dan MDRD menunjukkan persetujuan dengan kaedah standard , $p > 0.05$. Analisis keperluan pengubahsuain dos ubat menunjukkan terdapat satu kes yang melibatkan meropenem di mana pengubahsuain dos diperlukan berdasarkan kreatinin klearans urin 24 jam yang diukur tetapi tidak diperlukan oleh semua kaedah anggaran kreatinin klearans yang lain, kecuali kaedah Cockcroft-Gault diubahsuai. Secara keseluruhan, berdasarkan ketepatan anggaran dan konsistensi (kebolehulangan) serta keringkasan kaedah Cockcroft-Gault diubahsuai, ia merupakan kaedah yang boleh dipercayai untuk menilai fungsi buah pinggang pesakit yang mengalami fungsi buah pinggang yang tidak stabil. Kaedah anggran kreatinin klearans keadaan tidak stabil yang

lain (Jelliffe, Brater dan Jelliffe diubahsuai) merupakan pilihan kedua, kecuali kaedah Chiou kerana kaedah ini secara konsisten memberi anggaran kreatinin klearans yang lebih rendah dalam kedua-dua fasa pemerosotan dan pemulihan. Persamaan-persamaan anggaran kreatinin klearans keadaan stabil yang biasa digunakan patut dielakkan pada pesakit yang mengalami fungsi buah pinggang tidak stabil. Kaedah keadaan stabil cenderung untuk menilai fungsi buah pinggan secara berlebihan semasa fungsi ginjal merosot dan semasa pemulihan fungsi ginjal.

**COMPARISON OF EIGHT METHODS FOR ESTIMATION OF CREATININE CLEARANCE IN MALAYSIA PATIENTS WITH UNSTABLE RENAL FUNCTION**

## ABSTRACT

Unstable kidney function is a common complication in hospitalized patients and is associated with high mortality rate. Critically ill patients normally have fluctuating kidney function with serum creatinine changing from day to day. Creatinine clearance (Clcr) estimation is of great importance in daily clinical practice among critically ill patients with unstable kidney function. The Cockcroft-Gault method remained the most widely used method to estimate kidney function and to guide drug dosage adjustment. The Cockcroft-Gault equation was derived from conditions in which the serum creatinine was at steady state and it is not designed for patients with unstable kidney function. This study aimed to analyze the discrepancies of estimated creatinine clearance computed by Cockcroft & Gault, MDRD, CKD-EPI, Jelliffe, modified Jelliffe, Chiou, Brater, and an empiric estimating equation (modified Cockcroft-Gault) equations with 24 hours urinary creatinine clearance (standard control) in critically ill and unstable kidney function patients from local Malaysian population. This was a multicentre, prospective, observational study. A total of 43 patients from three public hospitals were recruited. During the early phase of unstable kidney function, the mean value of urinary creatinine clearance was 20.56±18.47 ml/min. Among the equations, only the modified Cockcroft-Gault method (20.12±17.19 ml/min) showed non-significant different with the urinary creatinine clearance ($p = 0.741$). A sub-set analysis on 23 patients with acute deteriorating

kidney functions was performed. The mean value of urinary creatinine clearance was 11.77±6.27 ml/min. Among the equations, only the modified Cockcroft-Gault (12.72±6.01 ml/min) showed non-significant different with the urinary creatinine clearance ($p = 0.843$). Sub-set analysis was performed on 20 patients with rapid improving renal functions and it revealed the mean value of urinary creatinine clearance was 30.66±22.53 ml/min. Among the equations, the Chiou method greatly underestimated the Clcr by approximately 34%, $p < 0.001$. Bland-Altman analysis was performed to determine the agreement between estimated Clcr to the standard urinary Clcr. During acute deteriorating kidney function, only modified Cockcroft-Gault method showed agreement with the measured urinary creatinine method, $p > 0.05$. Meanwhile, during rapid improving kidney function, the Jelliffe, Brater, modified Cockroft-Gault and MDRD method showed agreement to the standard method, $p > 0.05$. Drug dosage adjustment requirement analysis showed that one case involving meropenem by which dosage adjustment was needed based on the measured 24 hours urinary creatinine clearance but not required by all other creatinine clearance estimating methods except the modified Cockcroft-Gault method. In overall, owing to the precision of estimation and the consistency (reproducibility) as well as the simplicity of modified Cockcroft-Gault method, it should be the reliable method to assess kidney function in critically ill patients with unstable kidney function. Other non-steady state creatinine clearance estimating methods (Jelliffe, Brater and modified Jelliffe) should be the second option, except the Chiou method as this method consistently underestimating the creatinine clearances in both deteriorating and improving phases of kidney functions. The commonly used steady state creatinine clearance estimating equations should be avoided in critically ill patients with unstable kidney function. The steady state methods prone to overestimate the kidney

function during deteriorating kidney function and during the early recovery of kidney function.

# CHAPTER 1

# GENERAL INTRODUCTION

## 1.1 Introduction

Acute kidney injury (AKI) is defined as an acute decrease in renal function or glomerular filtration rate (GFR) in a manner of hours, days or weeks. It is a condition where the kidneys fail to perform its normal function and is associated with accumulation of metabolic waste products and fluid (Matzke, 1997; Nash, 2002; Ostermann, 2014).

AKI can be divided into three different categories, namely community acquired AKI, hospital acquired AKI and intensive care unit (ICU) acquired AKI. Among these three categories of AKI, ICU acquired AKI recorded the highest incidence, which is around 35 to 70%. This is followed by hospital acquired AKI, approximately 15 to 40%. Community acquired AKI is relatively uncommon, its incidence was recorded to less than 1% (Wonnacott et al., 2014; Bellomo et al., 2017; Jurawan et al., 2017).

The common risk factors for ICU acquired AKI include sepsis, septic shock, major surgery, multi-organ failure, hypotension (particularly those who require inotropic support), low cardiac output or receiving nephrotoxic drugs (i.e aminoglycoside). Its overall mortality rate was recorded as high as 30 to 90% (Chertow et al., 2005; Eknoyan, 2012; Nie et al., 2017). Meanwhile, volume depletion, hypotension, low cardiac output, nephrotoxic drugs and radio-contrast dyes are among the common risk factors for hospital acquired AKI. Hospital acquired AKI carries an overall mortality rate of 15 to 40% (Chertow et al., 2005; Eknoyan, 2012; Nie et al., 2017). Meanwhile, the community acquired AKI carries the lowest overall mortality rate of approximately 15%. The most common contributing factors include reduced or

poor fluid intake, dehydration, drugs like renin-angiotensin-angiotensinogen system (RAAS) blockers, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy, acute infection, trauma or rhabdomyolysis (Chertow et al., 2005; Wonnacott et al, 2014; Bellomo et al., 2017; Jurawan et al., 2017).

Regardless of the types of AKI, estimating one's renal function during AKI is always a challenge due to its daily fluctuation of serum creatinine (Jelliffe, 1972; Matzke, 1997). It is always desirable to estimate one's GFR at the bedside and the commonly used methods like Cockcroft-Gault method, MDRD method or CKD-EPI method requires a stable renal function. Therefore, these equations or methods do not work if the plasma creatinine is changing rapidly. Estimating one's renal function when serum creatinine is not at steady state will most likely overestimate the renal function by 10 to 40%. This will lead to masking effect of renal impairment as well as drug dosing error for renally excreted drugs that require dosage adjustment. (Bouchard et al., 2010; Chen, 2013; Mellas, 2016)

In order to overcome the pitfalls of unable to accurately estimating the renal function in patients with unstable kidney function, several mathematical methods were developed which claimed to be able to measure one's renal function in a more accurate manner when serum creatinine was fluctuating. These methods are known as the Brater's method, the Chiou's method and the Jelliffe's method. The drawbacks of these methods were that they were not robustly tested and no strong conclusion of their practical feasibility can be generated (Cockroft, 1976; Chiou, 1975; Brater, 1983; Jelliffe R., 2002).

## 1.2 Problem Statement

AKI is a common complication in hospitalized patients and is associated with high mortality rate. The incidence of AKI is markedly higher in critically ill patients and those admitted to ICU settings (Nash, 2002). An estimated 5 to 20% of critically ill patients experience an episode of AKI during the course of their illness and AKI receiving renal replacement therapy (RRT) has been reported in 4.9% of all admission to ICU (Metnitz et al., 2002). Critically ill patients normally have fluctuating renal function with serum creatinine changing from day to day (KDIGO: CKD, 2012) as well as dilution effects of parenteral solutions (in large quantities) on serum creatinine. Hence, the patient's GFR estimation is of great importance in daily clinical practice particularly among critically ill patients with unstable kidney function. Currently, to the best of our knowledge, there is no estimated GFR (eGFR) equations which have been validated in critically ill patients with unstable kidney function.

Over 95% of practitioners use Cockcroft-Gault equation to estimate creatinine clearance for dosage adjustment in patient with kidney disease as shown in a survey of 204 members of American College of Clinical Pharmacy (ACCP) Nephrology and Critical Care Practice and Research Network in 2009 (Heather AN., 2011). The Cockcroft-Gault equation was derived from conditions in which the serum creatinine was at steady state. It is the most widely used equation as most of the approved dosing information from the manufacturer of drugs was developed from pharmacokinetics studies using Cockcroft-Gault equation. Nevertheless, the Cockcroft-Gault equation is not designed for patients with unstable kidney function as serum creatinine changes lag behind the actual timing of the kidney insult, leading to overestimation of renal clearance by using a steady state equation.

Patients with unstable kidney function experience alterations in drug pharmacokinetics such as renal metabolism and clearance. Other aspects such as drug absorption, distribution and plasma protein binding are also impaired. Inappropriate drug dosing of patients with unstable kidney function is an important cause of adverse drug events. Drug therapy may not be effective or may be toxic if there were inappropriate drugs dosing based on false creatinine clearance estimation especially for drugs with narrow therapeutic indexes. Drug dosing in critically ill patients with unstable kidney function has been problematic. Several issues are unique in this population, including the rapid changes in serum creatinine and the time required to reach a new steady state concentration. Besides, the influence of aggressive volume resuscitation that ultimately led to increased volume of distribution is another challenge among the critically ill patients. The patients also experience problems of increase in creatinine secretion in early AKI and increased non renal clearance. The lack of evidence-based dosing and influence of renal replacement therapy further complicated the dosing adjustment for renally excreted drugs among the patients under critical care. Drug doses need to be adjusted appropriately with the correct assessment of kidney function to reduce toxicity (Kane et al., 2003). The ICU population is exceptionally vulnerable in a sense of under dosing of drugs, particularly anti-infective often always lead to poor response or mortality; meanwhile undesired adverse effects or permanent damage or even death may be arising secondary to overdosing. Under estimation of one's renal function may leads to under dosing of drugs and vice versa. This resulted in challenges in optimization of drug therapy in patients with unstable kidney function (Erstad, 2015).

### 1.3 Rationale of the Study

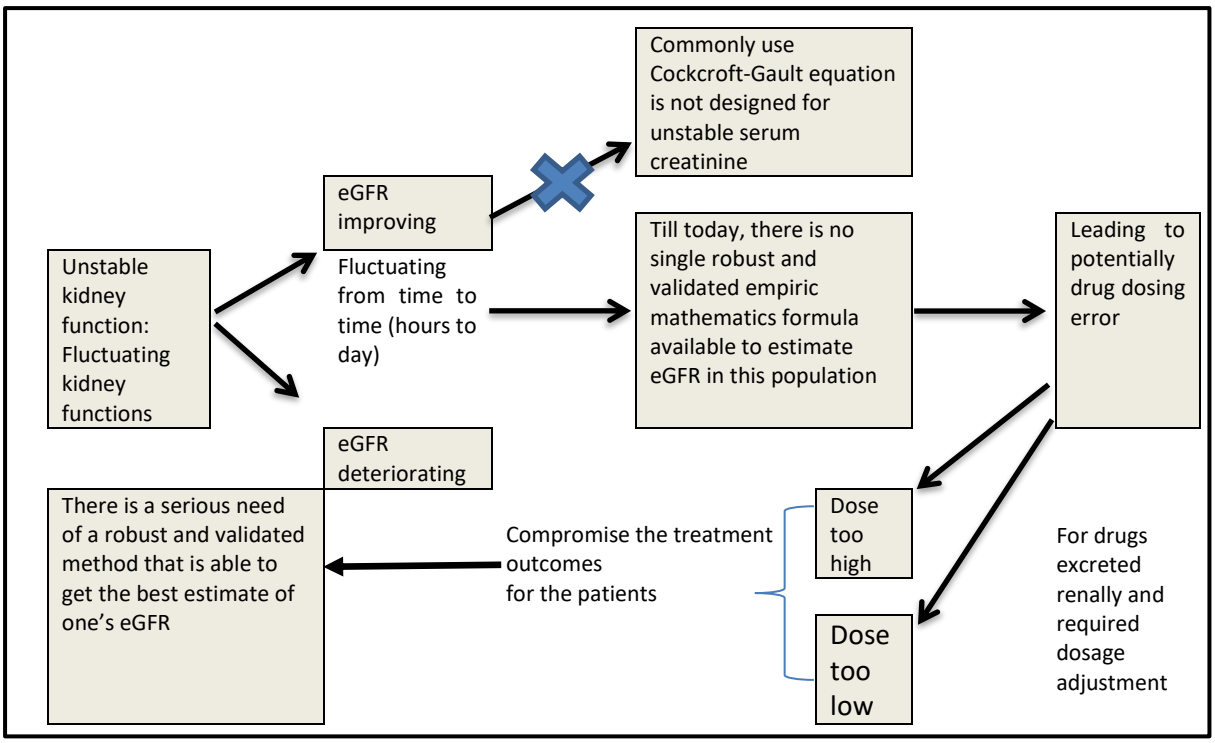


Figure 1.1 Rational of the study

Estimation of creatinine clearance has long been a problem in critically ill patients with unstable kidney function. The KDIGO guidelines stated that the creatinine clearance (ClCr) should be measured whenever possible in patients with unstable kidney function. It also stated that the serum creatinine concentration and creatinine clearance remain the best clinical indicators of one's renal function. The development of a rapid, accurate, safe, user friendly and inexpensive method of estimating creatinine clearance has a high clinical importance as employing isotopic methods (measuring kidney function using exogenous administered radio-isotope) is cumbersome and impractical. This study shall analyze the discrepancies of estimated creatinine clearance computed by Cockcroft & Gault, MDRD, CKD-EPI, Jelliffe, modified Jelliffe, Chiou, Brater, and an empiric estimating equation (modified Cockcroft-Gault) equations with 24 hours urinary creatinine clearance (standard control) in critically ill and unstable kidney function patients from local Malaysian

population. Equations that potentially to be used to assess one's kidney function during unstable kidney function phase such as Jelliffe, Modified Jelliffe, Chiou and Brater are complex and involving various steps in performing the calculation. Data from our previous retrospective study (Ng, 2014, Master of science thesis) based on local Malaysian population showed that the most commonly used estimation equation, Cockcroft-Gault showed approximately 25% to 30% higher ClCr when compared with Jelliffe method. The PICARD study (2010) revealed that Jelliffe equation was able to provide the closest estimation of one's ClCr with unstable kidney disease, but overestimating ClCr by 10%. From these findings, there is still a room for improvement in the effort of getting the nearest estimation to the actual ClCr. It is hypothesized that the empiric equation (which attempt to improve the accuracy of estimated ClCr) shall be a better alternative based on its simplicity.

A reliable and more accurate tool is needed in the estimation of creatinine clearance for the critically ill patients with unstable kidney function in order to guide dosage adjustment of renally excreted drugs. The 24 hours urine collection method remains the second best method of estimating one's GFR after the isotopic method. The 24 hours urine collection method or also known as timed urine collection is not invasive and does not involve exogenously administered substances such as inulin, iothlamate, iohexol or radioisotopes which are expensive, not readily available and not practical in daily use especially in intensive care setting. In addition, this method is indeed validated in critically ill patients (Blasco, 2011; Herrera-Gutie´rrez, 2007). As such, the 24 hours urinary creatinine clearance still offers values close to the real renal function of the patients (Rehberg, 1926; Stevens, 2006 & Endre 2011). However, the 24 hours urinary clearance method using two consecutive points of serum creatinine (amount of total urinary creatinine clearance divided by serum creatinine

concentration) was found to be producing highly variable and inaccurate in patients with rapidly improving renal function (Chow & Schweizer, 1985). In addition to that, the 24 hours urine method is not practical to be used in daily practice as it involves the collection of the patient's urine for 24 hours. Besides the problem in urine collection, this method is unable to give a very prompt estimation of kidney function. For patients under critical care with unstable kidney function, it is crucial to have a prompt estimation of kidney function for dosing adjustment (Piotr, 2019).

Josee Bouchard et al. (2010) reported in the Programme to Improve Care in Acute Renal Dysfunction (PICARD) study that the degree of over-estimation of GFR by Cockcroft-Gault was 80%; 4-variable modification of diet in renal disease (MDRD) was 33% and 10% with Jelliffe formula. The study also reported that the modified Jelliffe formula was closest to the reality by which it underestimates GFR by only 2%. However, the main limitation of modified Jelliffe equation is it was not robustly tested at larger population. The relative overestimation of GFR by Cockcroft-Gault and MDRD was reported to be even more prominent if the baseline GFR is higher. In addition, Cockcroft-Gault and MDRD overestimating the GFR in most patients with fluid accumulation.

Currently, to the best of our knowledge, there are no known accepted methods for accurately estimating GFR in patients with unstable kidney function globally. The current practice in estimating Clcr in ICU setting is using Cockcroft-Gault equation by incorporating data such as serum creatinine concentration, age, gender and body weight. A simple formula which requires only few inputs that are readily available from clinical laboratory data shall be an ideal solution. An accurate assessment of one's renal function is essential to optimize drug administration and other processes of care.

## 1.4 Aims and Objectives

There is a strong need to investigate if the differences of eGFR estimated with various methods are significant enough to influence the clinical judgment on proper dose titration. Besides, it is crucial to determine which method agreed best with measured 24 hours urinary creatinine clearance.

### 1.4.1 Primary objective

1. To derive a method to calculate Clcr more accurately when using two serum creatinine ($C_0$ and $C_{24}$) in patients with rapidly improving renal function.

2. To derive an improved method to estimate Clcr in unstable renal function (modified Cockcroft-Gault).

3. To compare the eight methods to estimate Clcr and compare with measured Clcr (using both improved method derived from primary objective 1 and the commonly used 2 points serum creatinine method).

### 1.4.2 Secondary objectives

1. To determine the level of agreement between calculated creatinine clearance based on different equations with measured 24 hours urinary creatinine clearance.

2. To evaluate the different in the drug dosing adjustment based on estimated creatinine clearances using Cockcroft & Gault, MDRD, CKD-EPI, Jelliffe, modified Jelliffe, Chiou, Brater, and an own empiric estimating equation (modified Cockcroft-Gault) equations compared to 24 hours urinary creatinine method (as the standard) for critically ill patients with unstable kidney function.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Kidney and its Function

Human kidneys are a pair of bean-shaped organs approximately 11 centimeters each found on the left and right sides of the retroperitoneal space. Normally the right kidney is slightly smaller and lower than the left kidney due to the position of the liver. (Glodny et al., 2009). The renal arteries responsible to supply oxygenated blood to the kidneys, meanwhile, the blood will exist through the renal veins. Approximately 10% to 20% of the cardiac output will be directed to the kidneys (Rafael, 2010). The kidneys are attached to ureter that directs the urine into the urinary bladder. The kidney weighs between 125g to 170g in adult males while around 115g to 155g in adult females (Walter, 2004). The structural and functional unit of the kidney is known as the nephron and each adult human kidney has around one million nephrons.

## 2.2 Urine Formation

The urine is formed through the processes of filtration, reabsorption, secretion and excretion (Totora & Gerald, 2010).

### 2.2.1 Filtration

Nearly 20% of the blood filtered under pressure through the walls of the glomerular capillaries and Bowman's capsule in the nephron. The glomerular filtration rate is approximately 125 mL/ min or equivalent to 180 litres per day. The total blood volume in human adult is between 7 to 8 litres, with the rate of filtration of 125 mL/min it means that the whole blood volume gets filtered for 20 to 25 times each day. The filtration process takes place in the renal corpuscle. It is a process

where large protein (including albumin) and cells are being retained while fluids and solutes with low molecular weights are filtered from the blood which formed the ultra-filtrate and eventually urine (Pocock, 2006; Totora & Gerald, 2010).

### 2.2.2 Reabsorption

The transportation process of molecules from ultra-filtrate into the peri-tubular capillary is known as reabsorption. 55% of water is reabsorbed in the proximal tubule. The sodium/glucose co-transporter is responsible to reabsorb the plasma glucose. At normal plasma glucose level, 100% of the glucose will be reabsorbed. Once the plasma glucose level exceeding 19.4 mmol/L all the sodium/ glucose co-transporter will be saturated and the glucose will be lost in the urine. Glucosuria will be detected at the plasma glucose of more than 8.9 mmol/L. Amino acids are reabsorbed at the proximal tubule via the sodium dependent transporter. Reabsorption takes place along the tubule of the nephron. The early proximal tubule is responsible to reabsorb 100% of glucose, 100% of amino acids, 90% of bicarbonate, 65% of sodium, 65% of chloride, 65% of phosphate and 65% of water. Only water will be reabsorbed at the thin descending loop of Henle. Sodium (10 to 20%), potassium, chloride, magnesium and calcium are reabsorbed at the thick ascending loop of Henle. Additional sodium and chloride are reabsorbed at early distal convoluted tubule. The collecting tubule will further reabsorb 3% to 5% of sodium and also responsible for the reabsorption of water (Tao L., 2013).

### 2.2.3 Secretion

Secretion is the reverse process of reabsorption. Substances like proton, creatinine, urea, hormones and drugs will be secreted into the collecting duct via the peri-tubular capillary network. This process is accomplished by active transport and passive diffusion (Totora & Gerald, 2010).

### 2.2.4 Excretion

Excretion is the final step in the processing of ultrafiltrate. The ultrafiltrate will be channeled out from the nephron into the collecting duct and eventually into the ureters where it is termed as urine (Totora & Gerald, 2010).

## 2.3 Functions of the Kidneys- Acid-base Balance

Acid base balance in human body is tightly controlled in order to maintain a normal range of extracellular pH between 7.35 to 7.45 and between 7.0 to 7.3 for intracellular pH. This is important in protecting the body's proteins (Adrogue., 2001). The mechanisms involved in maintaining the narrow ranges of pH include expelling carbon dioxide through ventilation system and acids elimination as well as bicarbonate reabsorption through the renal system (Rose, 2005). The bicarbonate is responsible for 36% of intracellular and 86% of extracellular fluid buffering activity (Adrogue, 2001). The kidneys play an important role in regulating the acid-base balance. They reabsorbed and regenerated all the filtered bicarbonate. The enzyme carbonic anhydrase catalyses the intracellular formation of carbonic acid from water and carbon dioxide in the renal tubular cells. The carbonic acid that is formed is then dissociated to proton and bicarbonate. The proton is secreted into the tubular lumen in exchange with sodium and the bicarbonate is reabsorbed into the capillary blood from the renal

tubular cells. The amount of bicarbonate that needed to be reabsorbed can indeed be calculated by multiplying the glomerular filtration rate with the extracellular fluid bicarbonate concentration (180L/ day GFR x 24 mEq/L $HCO_3^-$ = 4320 mEq/ day). Approximately 85% of the filtered bicarbonate will be reabsorbed at the proximal tubule while approximately 10% of the filtered bicarbonate will be reabsorbed at the loop of Henle and the distal tubule (Adrogue, 2001).

## 2.4 Functions of the Kidneys- Regulation of Osmolality

The kidneys regulate serum osmolality by controlling the amount of water in the body. Should there be a deficit of water or electrolytes, it will be compensated by increased intake of water through the stimulation of thirst centre and retention. On the other way, should there be an excess of water there will be increases in urinary excretion. The regulation of water excretion influences both the fluid volume and osmolality. In example, should an increase in osmolality secondary to diarrhoea or excessive sweating exists, it will trigger water retention and fluid intake mechanisms such as releasing the antidiuretic hormone or thirst centre to return osmolality to normal as well as restoring fluid volume. An increase in dietary sodium shall increase the plasma osmolality. This in turn will activate fluid retention and intake mechanism to expand the volume. The kidneys are the main route of sodium and water excretion, hence, they have an important role in regulating the body fluid osmolality and the extracellular fluid volume (Atherton, 2006).

## 2.5 Functions of the Kidneys- Hormone Secretion

The kidneys regulate a number of hormonal functions. Hormones that are secreted by the kidneys include erythropoietin, calcitriol, and renin. The kidneys are the main source of erythropoietin. In normal condition, erythropoietin is release as a response to low tissue oxygen saturation. Erythropoietin stimulates the production of red blood cells in the bone marrow. The replacement of erythropoietin was found to be able to reverse anaemia of chronic kidney disease (Turner, 2002; Toshiaki, 1994). Serum erythropoietin levels correlate inversely with haematocrit, haemoglobin and red blood cell counts. On the other hand, the erythropoietin was found to correlate positively with iron concentration. This explained the need to restore iron before the initiation of erythropoietin in anaemic patients secondary to long standing chronic kidney disease (Toshiaki, 1994). Calcitriol is released by the kidneys to promote intestinal absorption of calcium and the kidney reabsorption of phosphate. The kidneys involve in the final step of activation of Vitamin D, the conversion of hydroxylates 25-hydroxycholecalciferol to 1,25-dihydroxycholescalciferol, the active form at the renal proximal tubule. Failure in this step will leads to hypocalcemia and kidney bone disease of chronic kidney failure (Turner, 2002; Adriana, 2005). Renin is an enzyme secreted from the juxtaglomerular apparatus in response to reduced pressure at the afferent arterioles. This will in turn stimulate the sympathetic nervous system and changes in the composition of fluid at the distal convoluted tubule at the macula densa. Renin will regulate angiotensin and aldosterone levels. Renin generates angiotensin II that will cause the constriction of afferent arterioles of the glomerulus and therefore increase glomerular filtration pressure. The increasing angiotensin II hormone in return will produce systemic vasoconstriction and hypertension. This explains that renal ischemia will leads to systemic hypertension (Gutkin et al., 1969).

## 2.6 Functions of the Kidneys- Blood Pressure Regulation

The kidneys play an important role in regulating the long-term blood pressure control. Regulation of blood pressure is maintained primarily through the regulation of extracellular fluid compartment. Extracellular fluid compartment is depending on the plasma sodium concentration. The renin-angiotensin system plays an essential role in regulating the extracellular fluid volume. The renin is an important chemical messenger in the renin-angiotensin system. Renin regulates angiotensin II and aldosterone hormones, these hormones will increase the kidney's reabsorption of sodium chloride, increasing intravascular volume through sodium and water retention, thus raising the blood pressure (Wadei & Textor, 2012).

## 2.7 Types of Kidney Diseases

In general, there are two types of kidney diseases, namely, the acute and chronic types. Acute renal failure can be further classified into pre-renal acute kidney injury, functional acute kidney injury, intrinsic kidney injury, and post renal acute kidney injury. These injuries can be aroused from community acquired, hospital acquired or intensive care unit acquired (Eknoyan et al., 2013).

When there is evidence of kidney damaged with estimated glomerular filtration rate of less than 60 ml/min / 1.73 $m^2$ for a period of greater than 3 months, then it is categorized as chronic kidney disease. According to the KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease (2012), chronic kidney disease is defined as abnormalities of kidney structure or function for more than 3 months (Eknoyan et al., 2013).

### 2.7.1 Acute Kidney Injury (AKI)

Acute kidney injury (AKI) is defined as an abrupt reduction in kidney function and leading to accumulation of nitrogenous waste products such as urea and dysregulation of fluid as well as electrolytes. Abrupt change in this context refers to over a period of hours to days (KDIGO, 2012). In the past decades, many definitions have been used to define AKI, as many as 35 different definitions, making it difficult to compare patient populations across studies. Hence, in year 2002, the Acute Dialysis Quality Initiative (ADQI) workgroup developed the RIFLE (risk, injury, failure, loss, end stage renal disease) staging system (Kellum, 2002).

The incidence of AKI has been increasing over the past decades, giving the long-term adverse outcome. AKI is currently a growing health concern worldwide (Lameire et al., 2013; Siew & Davenport, 2015). AKI is a new consensus term to replace acute renal failure It is a clinical syndrome characterized by a rapid (in a matter of hours to day) reduction in kidney excretory capacity that leading to accumulation of nitrogenous waste products such as creatinine and urea, reduced urine output, electrolytes disturbances (increased potassium and phosphate) as well as water. The term AKI emphasize that a continuum of kidney injury exists and begins long before sufficient loss of excretory kidney function can be measured with standard laboratory tests. Besides, it also suggests a continuum of prognosis, by which, a small rise in serum creatinine is associated with increasing mortality, and an additional increase in mortality as creatinine concentration rises (Bellomo et al., 2004).

## 2.8 Factors Associated with AKI

Several risk factors have been identified associating with AKI for patients admitted to hospital. These risk factors include older age, comorbid diseases, proteinuria or existing chronic kidney disease, nephrotoxic agents exposures (Amphotericin B, aminoglycosides, non-steroidal anti-inflammatory drugs, excluding aspirin, radio contrast within 24 hours), major surgery (cardiac surgery, aortic surgery, hepatobiliary surgery), sepsis, fluid resuscitation, volume status (volume depletion as define as central venous pressure of < 6 cm of $H_2O$ or pulmonary capillary wedge pressure of < 8 cm $H_2O$) and requirement of vasopressor (except dopamine less than 5.0 μg/kg/min) (Chawla et al., 2005).

### 2.8.1 Age

The incidence of AKI increases with age, particularly those aged more than 70 years old. Observational studies conducted by Hilberman (1979), Corwin (1983), Ward (1996), Loef (2005), Barrantes (2008), Bagshaw et al., (2008), Bagshaw (2008), Abelha (2009), Thakar (2009), Hobson (2009) and Machado (2009) showed a positive correlation of age and the risk of AKI for patients admitted to hospitals. Results from these studies showed the risk of AKI was assessed and significant difference was found between groups. Meanwhile, Groeneveld (1991), Vivino (1998), Mangano (1998), Conlon (1999), De Mendonca (2000), Bove (2004), Hoste (2006) and Landoni (2007) reported age as one of the risk factors for AKI and they found a significant difference between group.

### 2.8.2 Co-morbid

The co-morbid conditions include hypertension, chronic kidney disease (Creatinine > 176.8 μmol/L for men and > 160 μmol/L for women), diabetes, hyperbilirubinemia (serum bilirubin > 2.0 mg/dL), morbid obesity (BMI > 30.0 $kg/m^2$), coronary heart disease, heart failure (NYHA III and IV), hypotension (MAP < 70 mm Hg or any vasopressor except dopamine less than 5.0 μg/kg/min) and liver disease. The presence of the mentioned co-morbid diseases is a strong risk factors for AKI. A significant difference between groups was reported in adjusted comparison by Ward (1996), Mangano (1998), Conlon (1996), Bove (2004) and Landoni (2007).

### 2.8.3 Severity of Disease

Ward (1996), Vivino (1998) and Hoste (2006) reported a strong correlation of severity of disease and the risk of AKI in in-patient setting. The authors observed that hospitalized patients, particularly patients admitted to ICU are often exposed to a number of nephrotoxic agents and radio contrast exposure. Antibiotics, proton pump inhibitors and non-steroidal anti-inflammatory drugs are the most common drugs given to this population. In addition, critically ill patients often required vasopressor to maintain an adequate mean arterial pressure after failing with fluid resuscitation. Persistent hypotension increases the risk of AKI.

### 2.8.4 Cardiac Surgery

AKI is common after cardiac surgery. Studies showed that the risk of AKI is higher in post cardiac surgery patients as compared to non-cardiac surgery patients. Observational studies conducted by Mangano (1998), Conlon (1999), Bove (2004), Bahar (2005) and Landoni (2007) revealed a high incidence of AKI in population post cardiopulmonary bypass surgery. The pathophysiology of AKI after cardiac surgery is complex and multifactorial (Bellomo, 2008). The following mechanisms of injury might be involved: microembolization, neurohormonal activation, exogenous and endogenous toxins, metabolic as well as hemodynamic and inflammation factors, ischemia–reperfusion injury and oxidative stress. These mechanisms of injury may be interrelated and synergistic. The consequence of these insults is a cascade of reflex changes within the kidney leading to a common presentation of AKI manifesting as impairment of renal function, persistent renal vasoconstriction, an exaggerated response to exogenous vasoconstrictors, and vascular endothelial and tubular epithelial cell death due to necrosis and apoptosis (Bellomo, 2008). Common nephrotoxic agents are antibiotics, such as glycopeptides and aminoglycosides, and non-steroidal anti-inflammatory agents. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) may cause renal efferent arteriolar vasodilation and its use is associated with AKI (O'Neal, 2016).

### 2.8.5 Drug Induced AKI

Drug induced AKI can happen when medications are given to an otherwise normal, healthy patients, however, injury is more prominent in the setting of several insults to the kidney which include disease in combination with drug. The mechanisms of drug induced nephrotoxicity can further classify as pre-renal, renal (intrinsic), glomerular injury, vascular injury and post-renal (Pannu, 2008).

### 2.8.5 (a) Pre-renal AKI

Decreased blood flow to the kidney can result in injury and it may be caused by several mechanisms. The most common cause is the reduction on effective intravascular volume from shock resulting in reduced perfusion pressure. Drugs typically cause pre-renal AKI by one of two mechanisms: either decrease renal blood flow or influence intra-glomerular hemodynamic (Chertow et al., 2005; Eknoyan, 2002; Makris, 2016).

The excessive use of loop diuretics and several cardiovascular medications are among the common drugs affecting blood flow. Loop diuretics can alter extracellular volume by causing excess volume depletion or reduced effective circulation. Cardiac medications can decrease cardiac output (drugs with negative inotropic effect, particularly in the setting of severe or decompensated heart failure) or change the systemic vascular resistance (which include antihypertensive medications which reduce systemic vascular resistance by inducing vasodilatation) (Chertow et al., 2005; Eknoyan, 2002; Makris, 2016).

The normal hemodynamic of the kidney is maintained, in part, by vasodilatation of the afferent or vasoconstriction of efferent arterioles. Increased renal vascular resistance or decreased trans-capillary pressure can happen after medications

that affect these vessels are administered. Vasodilatation of the afferent arteriole is partly caused by the effects of prostaglandins. Drugs that may decrease prostaglandin synthesis reduce the ability of vasodilatation of the afferent arterioles. The common drugs known to inhibit this synthesis are the non-steroidal anti-inflammatory drugs (NSAIDs) and the cyclooxygenase-2 (COX-2) inhibitors (Chertow et al., 2005; Eknoyan, 2002; Makris, 2016).

Vasoconstriction of the efferent arterioles is mediated through angiotensin II. Drugs that inhibit angiotensin II such as angiotensin converting enzyme inhibitors and angiotensin receptor blocker prevent effective efferent vasoconstriction, resulting in decreased trans-capillary pressure. This resulting in the kidney loss its ability to maintain sufficient perfusion pressure. Tacrolimus and cyclosporine, calcineurin inhibitors have been associated with pre-renal AKI, although the exact mechanism has not been well established. Both afferent and efferent vasoconstriction may be involved. Calcineurin inhibitors also were found to be associated with acute interstitial nephritis (Chertow et al., 2005; Eknoyan, 2002; Makris, 2016).

### 2.8.5 (b) Intrinsic Renal AKI

Drug induced intrinsic AKI can be caused by several mechanisms and is the result of injury to the renal tubules, glomerulus, vascular structures, interstitium, or the obstruction of the renal tubules. Acute tubular necrosis is common in critical illness. Tubular injury results most often pre-renal insults (prolonged hypotension) or from nephrotoxic agents. Intravenous contrast agents, aminoglycosides, amphotericin B, and the antiretroviral agents are most commonly associated with acute tubular necrosis. In the absence of AKI, acute interstitial nephritis is uncommon. It occurs in only 1% to 3% of all renal biopsy-proven case. In the presence of AKI, the incidence

is higher and accounts for 15% to 27% of cases. Interstitial injury is characterized by inflammatory infiltrated and edema within the interstitium. The clinical presentation is non-specific and may include fever and rash with laboratory evidence of eosinophilia; however, this “classic triad” occurs in only 10% to 30% of patients. Drug induced acute interstitial nephritis represents more than 75% of cases. Other causes include infections (5% to 10%), idiopathic (5% to 10%) or associated with systemic diseases (10% to 15%). Several medications have been associated with acute interstitial nephritis, including antimicrobial (penicillins, cephalosporins, sulphonamide, ciprofloxacin, vancomycin), NSAIDs, and COX II inhibitors, omeprazole, lansoprazole, phenytoin, valproic acid, cimetidine, ranitidine, diuretics and cocaine. Renal recovery is usually complete once the offending agent has been removed; however, it may take weeks to several months (Makris, 2016).

Acute interstitial nephritis is associated with the chronic use of calcineurin inhibitors is often irreversible. In addition to removing the offending agent, steroids may be useful in limiting the damage. However, steroid use remains controversial. Acute glomerular nephritis is associated with inflammation and proliferation of glomerular tissue that results in damage to the basement membrane, mesangium, or capillary endothelium. Non-drug causes of glomerular nephritis include systemic disorders such as lupus, hepatitis, and vasculitis. Drug associated glomerular nephritis may include NSAIDs, ampicillin, rifampicin, lithium, penicillamine, hydralazine, gold, mercury, and heroin. Fever, malaise, and/ or arthralgia may occur. Treatment includes removal of the likely agent and may include the use of immunosuppressant, which may limit the disease (KDIGO, 2012; Makris, 2016).

Injury to the renal vascular system is more likely to be caused by either microvascular or macrovascular disease than induced by drugs. AKI associated with

microvascular disease is usually associated with thrombotic thrombocytopenia purpura, haemolytic uremic syndrome, and HELLP (hemolyisis, elevated liver enzymes, and low platelet) syndrome. It is often the result of glomerular capillary thrombosis. AKI is associated with macrovascular disease is usually associated with renal artery occlusion or major abdominal aortic disease. Injury is often irreversible; it should be considered in patients with recent vascular procedures (KDIGO, 2012; Makris, 2016).

Intra-tubular obstruction is uncommon and can be associated with non-drug or drug causes. Non-drug causes include multiple myeloma and tumor lysis syndrome. Injury results from monoclonal light chains and uric acid that obstructs the tubule. Drug associated with intra-tubular obstruction can result from the calcium oxylate crystals associated with ethylene glycol ingestion (Chertow et al., 2005; KDIGO, 2012; Makris, 2016).

### 2.8.5 (c) Post Renal AKI

AKI associated with post renal causes is uncommon in critically ill patients because a bladder catheter is usually in place. If an obstruction is suspected, it should be ruled out by evaluating the catheter, or by placing one if none. The obstruction may be in the luminal wall or extrinsic to the urinary tract. To cause AKI from upper tract obstruction, the blockage must be bilateral or affect a single functioning kidney. Medications that known to cause tubular obstruction include acyclovir, methotrexate, sulfadiazine, foscarnet, indinavir, tenofovir, ad triamterene. The risk factors include pre-existing renal dysfunction and poor hydration. Renal ultrasonography is the gold standard test for diagnosis (Chertow et al., 2005; Eknoyan, 2002; Makris, 2016).

Table 2.1 Location, Mechanism of Injury, and Potential Causes of Drug-Induced AKI

| |
|---|
| Pre-renal<br>Hemodynamic alterations<br>• ↓ Cardiac output (example negative inotropic agents)<br>• ↓ Systemic vascular resistance (example vasodilators)<br>• ↑ Renal vascular resistance – NSAIDs, COX-2 inhibitors, cyclosporine, tacrolimus<br>• ↓ Transcapillary pressure – ACEi, ARB<br>Extracellular volume depletion – excessive diuretic use |
| Renal (Intrinsic)<br>• Acute tubular necrosis – Aminoglycoside, amphotericin B, contrast agents, cocaine, antiretrovirals (adefovir, cidofovir, foscarnet, and tenofovir)<br>• Acute interstitial nephritis – Antimicrobials (penicillin, cephalosporins, sulphonamides, ciprofloxacin,vancomycin, macrolides, tetracyclines, and rifampin), COX-2 inhibitors, NSAIDs, PPIs (omeprazole, lansoprazole, phenytoin, valproic acid, diuretics, cocaine, H2 receptor antagonists (cimetidine, ranitidine)<br>• Glomerulonephritis – NSAIDs, antimicrobial (ampicillin, penicillamine, rifampin), lithium, hydralazine, gold, mercury, heroin. |
| Post-renal<br>• Precipitation of drug in the renal tubules – sulphonamide, antiretrovirals (acyclovir, foscarnet, indinavir, tenofovir), methotrexate, sulfadiazine, triamterene, vitamin C at large doses |
| Bladder obstruction<br>• Anti-cholinergiccs |

## 2.9 Staging of AKI According to RIFLE Criteria

The RIFLE classification is based on serum creatinine and urine output determinants, and considers three severity classes of AKI (risk, injury and failure), according to the differences in serum creatinine and/ or urine output. RIFLE categorizes AKI into three grades of increasing severity and two clinical outcomes. For the acronym RIFLE, “risk” is defined as oliguria for more than six hours or an increase in serum creatinine to 1.5 times the baseline or greater. While renal function continues to worsen, the criteria for “injury” and “failure” are fulfilled (Kellum, 2002; Manjunath, 2001).

Clinical outcomes which are the “loss” and “end stage kidney disease” are defined by the need for renal replacement therapy for more than four weeks and more than three months respectively (Kellum, 2002). This definition could be easily applied if the baseline serum creatinine is known. However, there is a significant number of patients with unknown baseline serum creatinine. In these cases, shall there is no history of chronic kidney disease, the baseline serum creatinine should be calculated using the MDRD equation, assuming a baseline glomerular filtration rate of 75 mL/min/1.73m$^2$ (Manjunath, 2001).

Table 2.2 Criteria for AKI according to RIFLE

| RIFLE Class | Serum Creatinine Criteria / GFR | Urine Output Criteria |
|---|---|---|
| R | Increase to 1.5 folds or GFR decrease > 25% from baseline. | < 0.5 mL/kg/hour for 6 hours |
| I | Increase to 2 folds or GFR decrease > 50% from baseline. | < 0.5 mL/kg/hour for 12 hours |
| F | Increase to 3 folds, GFR decrease > 75% from baseline or serum creatinine ≥ 4 mg/dL (acute increase of at least 0.5 mg/dL) | < 0.3 mL/kg/hour for 24 hours or anuria for 12 hours |
| L | Complete loss of function for > 4 weeks | |
| E | Complete loss of function for > 3 months | |

## 2.10 Staging of AKI According to AKIN Criteria

According to emerging data from the Acute Dialysis Quality Initiative (ADQI) suggesting that a small change in renal function (an increase of serum creatinine by 0.3 mg/dL or greater) shall lead to worse outcomes. (McCullough, 2013). The ADQI later formed the Acute Kidney Injury Network (AKIN). AKIN (2007) defines AKI by using a staging system of 1 to 3, as a reduction in renal function that occurs over no more than 48 hours based on the measured serum creatinine and urine output. It is a later version of the RIFLE classification with some modifications. These modifications include the diagnosis of AKI is only considered after achieving a sufficient hydration