

Evaluation of Acute Kidney Injury in Intensive Care Unit

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1. Introduction

Acute kidney injury (AKI), impairment of kidney function requires special attention in intensive care unit's (ICU), because if multiorgan failure affect the kidney, it carries a greater risk for worse outcome and furthermore survivors have higher risk then normal population for chronic renal failure. It was reported that they also have higher mortality and morbidity rates compared to normal population (Kellum, 2008 & Shiffle, 2006).

Acute tubular necrosis (ATN) is the primary causes of AKI in hospital and ICU and sepsis, ischemic or toxic insults were reported as the most common reason for ATN. The rates of AKI have been reported in hospitalized patients to be between 3.2%-20% and in ICUs this rate rises up to 22% and even to 67% depending on the population studied and the definition used (Murugan 2011). Based on the administrative data, the incidence of severe AKI (defined requiring dialysis) from 1988 to2002 has increased from 4 to 27 per 100000 population. But fortunately in hospital mortality, has decreased from 41.3 to28 % ($p<0.001$) (Waikar, 2008). Likewise a progressive 2.8% annual increase in incidence of AKI and progressive 3.8% annual decrease in AKI associated mortality(95%CI:-4.7 to-2.12; $p<0.001$) was observed from 1996-2005 in a large database in Australia and New Zealand (Pisoni, 2008&Bagshaw, 2007). Despite the fact that mortality might be decreasing in ICU patients with AKI, it is still high and reported to be up to 43-88%. Mortality rate becomes even higher when patients require renal replacement therapy (Kellum, 2008).

Interestingly, it was reported that irreversible AKI requiring chronic dialysis therapy increased from 3.7% in 1984 to 18.2% in 1995 in surviving patients. Even higher number of patients (33-68%) at discharge whose kidney failed to recover and who needed long term dialysis. This changing renal outcome in the survivors of ICU acquired AKI cases might be related to increasing number of older patients, several co morbid conditions, more severe AKI cases than before and in addition, complication of the more aggressive renal replacement therapies currently used (Shiffle, 2006).

Since AKI in critical ill patients have high mortality rate and even if patients survive, they are at risk for End Stage Renal Disease (ESRD) and higher mortality than the normal population, it is important to recognize the clinical picture of AKI and to institute prevention as early as possible. Thus, physician should be alarmed and be ready for early intervention in this particular group of patients. With the introduction of the RIFLE

classification for the definition of AKI, the viewpoint of this subject has changed and now it is possible to be aware of patients with high risk for AKI (Bellomo 2004). Nevertheless recently several biomarkers have been introduced to diagnose AKI even before creatinine starts to increase (Waiker, 2008).

In this review, new perspective and favorable improvement of this subject will be discussed; furthermore definition, epidemiology, risk factors, biomarkers of AKI will be evaluated.

2. Definition

Patients in ICU comprise heterogeneous population, and around 30 different definitions were used to describe acute deterioration of renal failure, which both caused difficulties to interpret studies and to discuss the conclusions. Since even small changes in renal function makes prominent differences, it was suggested that re-evaluation of the definition of AKI was mandatory. For the consensus of the definition and improvement of the quality of studies on AKI, Acute Dialysis Quality Initiative (ADQI) group was established. They recommended the term of AKI instead of ARF, since spectrum of AKI is broader and covers different degrees of severity of the disease. In 2002, for a uniform definition of AKI, they described three categories for severity (Risk of ARF, Injury of the kidney, and Failure of kidney function) and two classes for kidney outcome (Loss of kidney function and ESRD), which is called shortly RIFLE criteria (Table 1) (Bellomo, 2004). Since AKI is not a stable condition, definition based on changes in function seems to be more suitable. Two measures to reflect kidney function have been recommended for the purpose of definition of AKI; changes in serum creatinine level and urine output. Importantly, these criteria were validated based on ability to distinguish the patients with higher risk for the worst outcome (death and requirement for renal replacement therapy).

The RIFLE criteria have been validated in more than 550,000 patients worldwide. Many studies confirmed that a rise in mortality rates occurred with progressing RIFLE criteria in ICU cases (Murugan, 2011). RIFLE criteria validated in a study on two Turkish tertiary hospital ICU population. This study also showed that increasing mortality rate with increase in severity, difference in mortality rate between stages was statistically significant ($\chi^2=15.037$, $p<0.001$) (Yegenaga, 2010).

Later on in 2007, ADQI group with worldwide collaboration of nephrologists and critical care societies developed Acute Kidney Injury Network (AKIN), which intends to improve worldwide coordination and provokes the development of uniform standards in the AKI area. RIFLE criteria were refined by this group and reported a new AKIN classification, which classified AKI in three stages (stages 1, 2, and 3) according to the degree of damage and outcome categories Loss and ESRD were removed (Mehta, 2007). The purpose of these modifications were to include a small but important group of patients with early and mild AKI who experience a change in renal function that is greater than physiological variation but less than the 50% increase required for the RIFLE criteria. Thus, an absolute increase in serum creatinine levels of at least 0.3mg/dl in 48 hours was recommended to include in stage 1. Patients who required renal replacement therapy (RRT) are classified as stage 3 AKI, regardless of their serum creatinine levels and urine output. Nevertheless there is no common worldwide guideline about the timing to initiate of RRT, using it as criteria to describe stage 3 may cause some misunderstandings. In particular, patients with underlying chronic kidney disease (CKD) may be missed by the original RIFLE criteria but not by AKIN since it counts even smaller changes in serum creatinine level. In addition, 48-hours time

	Serum Creatine Criteria	Urine output criteria
RIFLE class		
Risk	Serum creatine increase to 1.5-fold OR GFR decrease >25% from baseline	<0.5ml/kg/h for 6h
Injury	Serum creatine increase to 2.0-fold OR GFR decrease >50% from baseline	<0.5ml/kg/h for 12h
Failure	Serum creatine increase to 3.0-fold OR GFR decrease >75% from baseline OR serum creatine $\geq 354\mu\text{mol/l}$ ($\geq 4\text{mg/dl}$) with an acute increase of at least $44\mu\text{mol/l}$ (0.5mg/dl)	Anuria for 12h
AKIN Stage		
1	Serum creatine increase $\geq 26.5\mu\text{mol/l}$ (0.3mg/dl) OR increase to 1.5-2.0-fold from baseline	<0.5ml/kg/h for 6h
2	Serum creatine increase ≥ 2.0 - 3.0 fold from baseline	<0.5ml/kg/h for 12h
3	Serum creatine increase >3.0-fold from baseline OR serum creatine $\geq 354\mu\text{mol/l}$ ($\geq 4.0\text{mg/dl}$) with an acute increase of at least $44\mu\text{mol/l}$ (0.5mg/dl) OR need for RRT	<0.3ml/kg/h for 24h OR anuria for 12h OR need for RRT

Table 1. Two definitions of AKI

interval for the diagnosis of AKI was introduced to ensure that the process is acute. Unlike RIFLE, in AKIN criteria there has been an attempt to resolve some easily reversible causes of azotemia (for example, volume depletion and urinary obstruction). AKIN criteria declare that diagnosis based on the urine criterion alone will require exclusion of urinary tract obstructions and other easily reversible causes of decreased urine output.

Determination of baseline renal function: Since AKI was defined as rapid decline in renal function from baseline levels, it is important how to measure baseline renal function. The baseline serum creatinine level has been recommended for use as a marker to reflect the renal function. The baseline serum creatinine value has been estimated in various ways, such as the serum creatinine level on hospital admission, the minimum creatinine level during the hospital stay, the serum creatinine value estimated from the MDRD calculation (assuming estimated $\text{GFR} = 75\text{ml/min}/1.73\text{m}^2$) or the lowest value among these (Ricci,

2011). The choice of estimation technique used to obtain the baseline creatinine value has a marked effect on the prevalence of AKI, severity of disease, and mortality risk associated with various stages of AKI. When pre-morbid renal function is not known ADQI group has recommended back-estimation of the baseline serum creatinine level value using the MDRD formula. In a study, involving 4,863 hospitalized patients, investigators studied the performance of these three potential surrogates for the baseline serum creatinine level and they concluded that all three surrogates resulted in bidirectional misclassification of AKI. Although the use of serum creatinine level at admission found to be more specific in this study, this parameter had the lowest sensitivity (38.9%) for diagnosis of AKI (Siew, 2010).

Subgroup analysis of data from the Beginning and Ending Supportive Therapy for the Kidney (BEST) study also compared observed baseline serum creatinine levels with MDRD back-estimated values to determine the RIFLE class. They found that MDRD back-estimated serum creatinine value performed reasonably well for the determination of the RIFLE categories when pre-morbid renal function was near normal, but should be cautiously used in patients with suspected CKD (Bagshaw, 2009).

As a conclusion investigators should make every effort to find out true baseline creatinine level before using any estimated values. An appropriate baseline serum creatinine value should express normal renal function of patients, such as outpatients serum creatinine level measured within the past year (preferably in the past 3 months). When an outpatient serum creatinine level is not available, serum creatinine level on admission to hospital or ICU could be used as a second choice. However, use of admission serum creatinine level is specific but insensitive, and may underestimate the incidence of AKI.

Which classification is better RIFLE or AKIN? Based on the studies to compare these two classifications; AKIN did not seem to show any improvement in the sensitivity and predictive ability of the definition and classification of AKI. Acute Physiology Score (SAPS)3 database in 2009 re-evaluated and compared the performance of the RIFLE and AKIN criteria (Joannidis, 2009). They concluded that RIFLE seems to be more sensitive for diagnosing AKI and to have a greater ability than AKIN criteria to predict the mortality. These data confirm that neither classification offers clear advantage over the other; and both systems still have some limitations. Similarly Bagshaw et al. compared AKIN classification and RIFLE criteria in 120,123 critically ill patients during the first 24 hours after admission to the ICU (Bagshaw, 2008). They concluded that AKIN classification did not improve the sensitivity and predictive ability of RIFLE criteria for the definition and classification of AKI in the first 24 hours in ICU. Based on these large database studies there is no evidence about superiority of any of these classifications. Both criteria can be used for the evaluation of critically ill patients, as long as the clinician is aware of the limitations mentioned above.

3. Etiology and risk factors for AKI

Early detection of AKI in ICU is crucial to perform early intervention and prevent further complications, thus it may be lifesaving to determine the risk factors for the impairment of the renal function.

The Program to Improve Care in Acute Renal Disease (PICARD) is prospective observational extensive cohort study, which was done in USA from 1999 to 2001 (Mehta,

2004). This study revealed that, etiology of AKI was ATN (acute tubular necrosis) in 50% of cases with no specific determined cause. The next most common etiologies included nephrotoxin administration (26%), cardiac disease (20%) including myocardial infarction, cardiogenic shock, and congestive heart failure, ATN from hypotension (12%), sepsis (19%), unresolved prerenal factors (16%) and liver disease (11%). They found that predictors of mortality using proportional hazards Cox regression at the day of diagnosis of ARF were age, BUN, liver failure. At the day of consultation; age, Log urine output, creatinine (<2mg/dl), BUN, liver failure, ARDS (acute respiratory distress syndrome) and platelet count were related to mortality. When the day renal replacement therapy started, the predictive factors for survival were found as age, platelet count, liver failure, sepsis or septic shock. Oliguria, sepsis, respiratory failure, and hepatic failure would be consistently associated with mortality in AKI (Chertow, 2006).

The largest cohort with most participant of AKI to date was the Beginning and Ending Supportive Therapy for Kidney (BEST) study (Uchino, 2005). Out of 29,269 critically ill patients, there were 1,738 (5.7%) patients with AKI. The most common cause of AKI was septic shock (47.5%), followed by major surgery (34%), cardiogenic shock (27%), hypovolemia (26%) and nephrotoxin administration (19%). In-hospital mortality varied from 50.5% to 76.8% between centers. A multivariate logistic regression model to identify independent correlates of in-hospital mortality yielded several previously identified risk factors, including delayed diagnosis of AKI, age, sepsis, and known disease severity score that included BUN and urine output, which are consistent with the previous studies.

Based on the previous reports; most common and complicated cause of AKI in ICU was found as sepsis and its prevalence have been reported to be 9-40% (Brivet, 1996 & Liano, 1998 & Bellomo, 2008). Therefore, we prospectively evaluated 257 patients with sepsis or systemic inflammatory response syndrome who were admitted to the surgical and medical ICU during 12 months in 2001 to determine the risk factors for acute renal failure (ARF) development (Yegeenaga, 2004). In this study, ARF was defined as serum creatinine level >2 mg/dL, based on this definition out of 257, twenty-nine (11%) patients were diagnosed as ARF. Mortality rate was 72% in patient with sepsis and ARF and in those with sepsis without ARF this rate was found as low as to 24%. Multivariate logistic regression analysis of data showed that older age (OR:1.1, CI:1.03-1.13) serum bilirubin >1.5 (OR:9.7, CI:1.65-60.3), higher baseline serum creatinine level (OR:1.02, CI:1.007-1.04), and higher central venous pressure (CVP) (OR:1.5, CI:1.26-1.80) were predictive for the development of ARF (Yegeenaga, 2004). It was mandatory to evaluate fluid status of these patients, since it was found that CVP is an independent risk factor for the development of AKI (Van Biesen & Yegeenaga, 2004). And subgroup analysis of these patients revealed that higher colloid fluid loading for the first 3 days (2037 ± 1681 vs 1116 ± 1220 , $p < 0.03$) and lower diuresis (1347 ± 649 vs 1849 ± 916 mL, $p = 0.005$) was associated with poor outcomes and in addition interestingly the fraction of inspired oxygen (FiO₂) needed to be increased significantly on the second day of sepsis in the ARF group but remained unchanged in non ARF group. These patients developed ARF despite further fluid loading and in addition, respiratory function deteriorated. Against the classical knowledge; this study brought up the idea that in critically ill patient fluid loading should be performed in cautious. It is more likely that in dehydrated patients fluid loading can prevent ARF development but in critical ill patients

with sepsis it might bring more risk for ARF and also to increase the mortality rate (Payen, 2008).

A similar study was designed previously for the Turkish ICU population of two tertiary hospitals, and RIFLE criteria were used for the definition of AKI (Yegegenaga, 2010). In this Turkish ICU population, AKI incidence was 56,8% including Risk of RIFLE, and mortality rate was 65% in AKI and and it was found 35% in non AKI group. In this study it was observed that mortality rate was correlated well with the severity of RIFLE criteria; in the risk group 56%, in injury 68%, and in failure it was found as 72%. Multivariate logistic regression revealed that unlike the previous study age and serum bilirubin level were not significant anymore, but SOFA score (OR: 1.49, CI:1.085-2.205, $p=0.045$), baseline serum creatinine level (OR: 1.87, CI:1.391-2.520, $p<0.001$), and every 1 liter of extra positive fluid balance (OR: 1.56, CI:1.029-2.373, $p=0.036$) were independent risk factors for AKI. This study also brought up the importance of fluid overload in critically ill patients with sepsis; despite more vasopressor use and more fluid resuscitation, kidney damage starts very early and that is difficult to reverse. Previously in this particular population fluid loading was known as early intervention, but based on the observation in this and in some other recent reports fluid therapy should be performed cautiously. It is claimed that fluid overload may increase intra-abdominal pressure, leading to abdominal compartment syndrome, which has been recently recognized as an important cause of AKI in critically ill patients (Schrier, 2004). Furthermore fluid overload has been demonstrated to cause other organ failure in addition to kidney in ICU patients (Malbrain, 2005); for example impairment of cardiac function, worsens the lung injury (Essen, 2002).

4. Biomarkers

The reduction in glomerular filtration rate (GFR) is the main abnormality which is responsible for the clinical picture of AKI. Since serum creatinine level (SCr) is negatively correlated with GFR value, SCr level has been used worldwide as a marker to estimate renal function for years. But it is understood now that creatinine may not be appropriate marker for couple of reasons to measure the GFR in AKI. Addition to tubular secretion; there are some factors which effect serum creatinine concentration for example; age, sex, muscle mass, metabolism of creatinine, and volume status. Therefore the measurement of SCr level only has very limited utility to evaluate total kidney function. It was understood that serum creatinine value is neither perfectly sensitive nor specific as a biomarker to determine GFR value. However Cystatin C was reported recently as the best alternative to SCr as an endogenous GFR marker and also it is able to predict AKI 1-2 days earlier than SCr. Cystatin C is a low molecular weight protein produced by all nucleated cells that is freely filtered by the glomerulus and then reabsorbed and metabolized by the proximal tubule (Herget-Rosenthal, 2005). Serum levels of Cystatin C are dependent not only on clearance but also on production rate and acute changes in volume of distribution. Higher dose of corticosteroid and hyperthyroidism may increase serum Cystatin C level and it may be decreased by hypothyroidism.

However, tubular cell injury may precede but not always lead to a reduction of GFR. The relationship between functional and structural changes in the kidney is inconsistent. For instance, in sepsis, changes in kidney function might be severe but in contrast histological

findings may not be clear. The earliest sign of ischemic or nephrotoxic AKI may not be decreasing in GFR level, therefore in this particular condition biomarkers should be able to identify tubular injury even before GFR falls and increasing in serum SCr level. Furthermore early identification of kidney injury will be critical for future developments in treatment or prevention of AKI (Cruz, 2010).

Several more biomarkers of AKI have been introduced recently, Neutrophil Gelatinase-Associated Lipocalin (NGAL) also known as Lipocalin-2 or siderocalin is one of the best studied biomarker of AKI to date. And it is rapidly up-regulated in the blood and in urine post-AKI. It was reported that; even though Cystatin C seems to be a better marker for AKI than SCr, Urine NGAL is superior to Cystatin C for earlier detection of AKI. In fact, cystatin C is mainly a marker of clearance, and its serum concentration may increase only after the GFR begins to decrease. Unlikely, NGAL which is rapidly induced in kidney tubule cells in response to ischemic injury, and its appearance in urine and serum is independent of the GFR but is highly predictive of a subsequent decline in GFR (Mishra, 2003).

Another promising biomarker is KIM-1, a type-1 transmembrane glycoprotein that is highly expressed in proximal tubule cells after ischemic and nephrotoxic injury. In a study with patient undergoing cardiac surgery, urine KIM-1 levels peaked 12 hours after injury in AKI and predicted the need for dialysis or mortality in hospitalised patients. KIM-1 seems to be more specific to ischemic and nephrotoxic kidney injury than NGAL and it is not significantly affected by chronic kidney disease or urinary tract infection (Liangos, 2007).

A pro-inflammatory cytokine IL-18 was also reported to be up-regulated and easily detected in the urine of animals with ischemic AKI. In a study, urine IL-18 levels were found markedly increased in patient with AKI but not in the patients with urinary tract infection, chronic kidney disease, nephritic syndrome, and prerenal failure. Urinary IL-18 showed sensitivity > 90% and specificity > 95% for the diagnosis of AKI (Parikh, 2008). Both urine IL-18 and NGAL were found as sequential predictive biomarkers of AKI in children undergoing cardiac surgery. The patients in whom AKI developed 2-3 days after surgery, urine NGAL peaked at 25 fold within 2 hours and declined 6 hours after surgery, whereas urine IL-18 levels peaked 12 hours after surgery (Parikh, 2006).

5. Conclusion

Since AKI increases mortality rate and significantly worsens patients' outcome, it is important to determine the patient with risk for AKI in ICU. The consensus has been achieved for the definition of AKI. This definition focuses on the association of hospital mortality, instead of renal failure requiring dialysis or clinical syndrome defined by pathology. Every patient who is admitted to the ICU should be evaluated and categorized based on the creatinine level. Furthermore, close follow-up of renal function is crucial. Recently introduced biomarkers can be used for early diagnosis of AKI even before SCr level starts to increase. During treatment of these patients intensivists should be alert against fluid overload which is described as an independent risk factor to develop AKI.

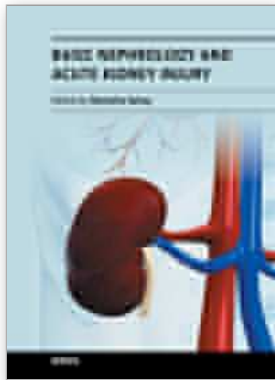
6. References

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Basic Nephrology and Acute Kidney Injury

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The first section of the book covers the basics of nephrology and second section focuses on acute kidney injury. This easy to reference text examines the physiological and biochemical aspects of renal diseases - all in one convenient resource. Experts in the field discuss topics of increasing concern in nephrology including newer methods of assessing renal function. The field of acute kidney injury in nephrology is a rapidly evolving one with research translating into clinical guidelines and standards. This text brings together experts to provide an authoritative reference for management of AKI in various clinical settings. Pregnancy related AKI is an important entity which has also been discussed in detail. The recent advances in the field of critical care AKI have been incorporated as well and help the reader to update their knowledge.

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