

Acute Renal Failure : Classification and Management Strategies

M. S. Amaresan

Introduction

Over the last few years considerable initiative has been taken towards better understanding of acute renal failure beginning with revision of the terminology itself as acute kidney Injury (AKI). The term AKI has been favored on the basis of the fact that the condition does not always result in kidney failure. AKI is a common condition associated with increased morbidity and mortality, yet a reversible

Table I : Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) Classification

Class	Glomerular filtration rate criteria	Urine output criteria
Risk	Increase in Serum creatinine $\times 1.5$ GFR decrease $> 25\%$	< 0.5 ml/kg/hour $\times 6$ hours
Injury	Increase in Serum creatinine $\times 2$ GFR decrease $> 50\%$	< 0.5 ml/kg/hour $\times 12$ hours
Failure	Serum creatinine $\times 3$, or serum creatinine ≥ 4 mg/dl with an acute rise > 0.5 mg/dl GFR decrease $> 75\%$	< 0.3 ml/kg/hour $\times 24$ hours, or anuria $\times 12$ hours
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks	
End-stage kidney disease	End-stage kidney disease > 3 months	

condition, if identified early and aggressively managed. Drawing of evidence based management guidelines has been impeded by the lack of uniform and well-defined criteria for describing the condition. This has made it impossible to analyse the outcome data of the various published data in a meaningful way. This article proposes to give the consensus definition and classification of AKI, the etiological classification of AKI, the scope for prevention of AKI and the rethinking on the mode of renal replacement therapy (RRT) for AKI.

AKI is defined by an abrupt (within 48 hours) increase in serum creatinine, resulting from an injury or insult that causes a functional or structural change in the kidney. The Acute Dialysis Quality Initiative (ADQI) represents the efforts of a workgroup to develop consensus and evidence based statements in the field of AKI. A consensus definition of AKI evolved by them is by using a set of criteria –RIFLE ¹

Rifle Criteria

A revision of the criteria was proposed by the Acute Kidney Injury Network (AKIN) - a group representing members of Acute Dialysis Quality Initiative, nephrology and critical care societies.

The proposed diagnostic criteria for AKI is an abrupt (within 48 hours) reduction in kidney

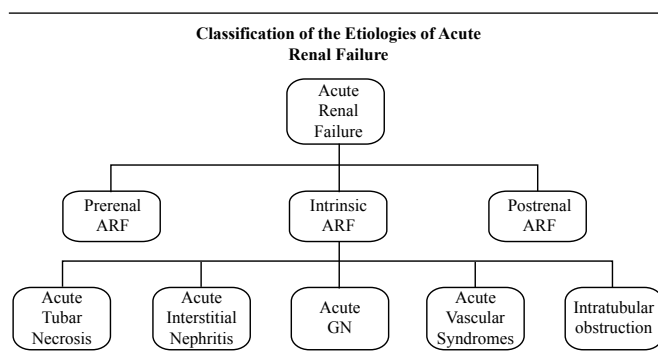
function defined as an absolute increase in serum creatinine (level of > 26.4 mmol/L (0.3 mg/dl) OR a percentage increase in serum creatinine level of $> 50\%$ (1.5 fold from baseline) OR a reduction in urine output (documented oliguria of < 0.5 ml/kg/hour for > 6 hours. (These criteria should be applied in the context of the clinical presentation and following adequate fluid resuscitation when applicable.)

Revised Rife Criteria

Class	Serum creatinine criteria	Urine output criteria
Risk	Increase of > 26.4 mmol/L (0.3 mg/dl) Or to 150 -200% of baseline (1.5 to 2.0 fold)	< 0.5 ml/kg/hour > 6 hours
Injury	Increase to > 200 -300% of baseline (> 2 -3 fold)	< 0.5 ml/kg/hour > 12 hours
Failure	Increase to $> 300\%$ of baseline (> 3 fold;or serum creatinine > 354 mmol/l (4.0 mg/dl) with an acute rise of atleast 44 mmol/l (0.5 mg/dl)	< 0.3 ml/kg/hour for 24 hours, or anuria for 12 hours

While retaining the emphasis on changes in serum creatinine and urine output as in RIFLE classification, the Loss and End Stage renal Disease categories were removed, as they are outcomes of AKI itself. Stage 1 criteria represent the new diagnostic criteria of AKI. Only one criterion (creatinine or urine output) needs to be fulfilled to qualify for a stage. Patients who receive RRT are considered to have met the criteria for Stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

This staging system for AKI is intended to define the degree of renal dysfunction at the time of diagnosis. Urine output was included as a diagnostic criterion as in intensive care patients it reflects renal dysfunction before the onset of changes in serum creatinine. However the hydration status, use of diuretics and presence of obstruction can influence urine volume.



Classification of AKI by Etiology

AKI can be classified by its etiology into prerenal, renal (intrinsic) and postrenal failure.

Prerenal AKI occurs in the clinical settings leading to volume depletion, decreased effective blood volume (congestive heart failure, cirrhosis, nephrotic syndrome, sepsis), renal vasoconstriction (hepatorenal syndrome, NSAID associated), altered renal hemodynamics (ACEI & ARB associated) and increased renal vein pressure (Abdominal compartment syndrome). Prerenal AKI should be anticipated in trauma patients, post liver transplant, mechanical limitation of abdominal wall caused by tight surgical closure or burn injuries, bowel obstruction, pancreatitis. A prospective study by Hou et al found prerenal azotemia to be the single most common cause of AKI in a medical surgical hospital.² Liano found prerenal AKI responsible for 48% of community acquired AKI and 58% of hospital acquired AKI.² Volume depletion and congestive heart failure increased the odds ratio of hospital acquired AKI by 9.4 and 9.2 fold respectively.² Not only is prerenal azotemia common but also it is potentially reversible.

Post renal failure is due to obstructive pathology that may be extrinsic (retro peritoneal, pelvic) or intrinsic (blood clot, calculus, carcinoma), upper or lower (prostate, urethral stricture, Neurogenic bladder, bladder carcinoma). In several series, obstructive pathology is encountered in 2% to 10 % of all cases of AKI.² The cause and incidence of obstructive pathology depends upon the age of

the patient and more common in selected patient population. It is often amenable to treatment and hence should be considered in each case of AKI.

The incidence of AKI is still on the rise. However there is a change in the epidemiological scenario with the aging population, greater frequency of critical illness, more aggressive diagnostic interventions (Contrast nephropathy), more frequent admissions in intensive care units, more aggressive cardiovascular and oncology surgeries and chemotherapy, rising incidence of infections like HIV, imported malaria, leptospirosis and as impact of newer therapies in ICU and expanding transplants- bone marrow, heart, lung. other nonrenal organs and combined organ transplants.

The frequency with which renal causes are encountered in patients with AKI varies from 25% to 80%. In a series of pediatric patients, 50% of all cases of AKI were attributed to renal parenchymal disorders as glomerulonephritis and hemolytic uremic syndrome. Acute tubular necrosis occurs due to prolonged prerenal failure (renal ischemia), nephrotoxins and pigmenturia (myoglobinuria, hemoglobinuria).

Management of AKI

AKI is a morbid condition- its clinical manifestations are not limited to the kidney. It is an inflammatory state and a systemic disorder. The systemic consequences of AKI are mediated by:³

The acutely uremic state: leading to metabolic derangements (carbohydrate, lipid, amino acid and protein metabolism), endocrine alterations (insulin resistance, hyperparathyroidism) and metabolic acidosis.

The injured Kidney: inducing a proinflammatory state with release of and impaired catabolism of cytokines (IL6, IL8, IL10), activation of immunocompetent cells and release of humoral factors promoting distal organ injury. Thus there is activation of coagulation cascade, increased norepinephrine, angiotensin II, endothelin, platelet activating factor, tumor necrosis factor, toll like

receptors and apoptosis especially in septic AKI.

The RRT: hemodynamic factors, loss of nutrients, activation of protein catabolism and induction of inflammatory reaction.

It thus contributes to multiorgan dysfunction. The long-term consequences of AKI are not benign. AKI is emerging as one of the causes of chronic kidney disease leading to End Stage Kidney Disease. Of 245 children treated for AKI, 174 survived. 16.6% of the survivors had chronic kidney disease over a 3 to 5-year follow up.⁴

The morbidity and mortality of AKI is closely linked to the time of its recognition and intervention Hence management strategies should include measures to prevent AKI atleast in identifiable people at risk, early identification of AKI and aggressive correction of the underlying cause besides early RRT when indicated. Early recognition of AKI and institution of corrective measures will ensure reversal to normal.

Prevention of AKI

Ideal management of the condition is thus its Prevention. At risk for AKI are the older age group, diabetics (especially if uncontrolled), those with hyperuricemia, dyslipidemia, hypertension, renal disease, heart failure, sepsis, multiple myeloma, volume depletion. and on concomitant nephrotoxic medications – aminoglycosides, diuretics, mannitol, vancomycin, amphotericin B, tacrolimus. Risk factors for AKI in the intensive care unit are myocardial dysfunction, liver failure, endothelial dysfunction, coagulation abnormalities, rhabdomyolysis, hemolytic uremic syndrome, ARDS, bacteremia and endotoxemia, sepsis and septic shock.

Prevention of Contrast Induced nephropathy (CIN)

Contrast media (CM) are being widely used for various radiological procedures. CM are responsible for 11% of hospital acquired AKI. It is the third most common cause of AKI after impaired renal

perfusion and use of nephrotoxic medications. Care should be taken when using the contrast media in patients at risk for AKI. Metformin is reported to cause lactic acidosis associated with AKI in patients with Type II diabetes. A meta analysis by the Cochran library with pooled data from 176 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 35619 patient years of metformin use or in 30002 patient years in the non metformin group.⁵ However the Food and Drug administration has recommended that metformin should be withheld the day of the contrast procedure and for further 2 to 3 days. Adequate control of glucose should be ensured pre and post procedure. Pre procedure statin use was associated with significant reduction in Contrast induced nephropathy in two retrospective studies. Larger studies are needed to clarify on the benefits. For the present, statins should be continued.

Reduction in the risk of CIN involves minimizing the volume of contrast media used, preventing repetitive exposure to contrast media in a short period of time, avoiding use of high osmolality contrast agents in high risk patients. Though isoosmolar and low osmolar contrast media are replacing the high osmolar contrast media, their superiority has not been supported by the various studies except the Nephrotoxicity in High Risk Patients Study of Isoosmolar and Low Osmolar Non ionic Contrast media (NEPHRIC) trial.⁶

Practical recommendations

All patients receiving contrast should be evaluated for their risk of CIN. All patients receiving contrast should be in optimal volume status at the time of exposure to contrast. Urine output is a reflection of the volume status and should be monitored before and after contrast exposure. It should not be pharmacologically enhanced by diuretics.

Pharmacological prophylaxis with N acetylcysteine has shown equivocal benefits Higher dose of 1200 mg bid for 4 doses has been recommended. Low osmolality contrast media are recommended for all

patients. Drugs that adversely affect renal function should be withheld prior to and immediately after the procedure. In all high risk patients, a follow up serum creatinine should be obtained at not less than 24 hours or more than 72 hours following contrast exposure.

Early Recognition of AKI

Novel biomarkers of Acute kidney injury have been identified. If these are utilized in the at risk situations for AKI, they will assist early institution of corrective measures. As they represent sequentially expressed biomarkers, it is likely that the AKI panels will be useful for timing the initial insult and assessing the duration of AKI. Based on the differential expression of the biomarkers, it is also likely that the AKI panels will distinguish between the various types and etiologies of AKI.

Novel biomarkers of Kidney Injury

Cystatin C, Kidney Injury Molecule -1 (KIM-1), Neutrophil Gelatinase Associated Lipocalin (NGAL), Na⁺ / H⁺ Exchanger Isoform 3 (NHE 3), N-Acetyl Glycosaminidase (NAG), γ - Glutamyl transpeptidase, α and π Glutathione S transferase.

And Interleukin-18 are some of the biomarkers of AKI.

The biomarkers of promise include a plasma panel (NGAL and cystatin C) and a urine panel (NGAL, IL-18 and KIM-1).

The amount of NGAL in urine (uNGAL) at 2 hours after cardiopulmonary bypass is the most powerful and independent predictor of AKI.⁷ In a prospective study of 140 critically ill children, Urinary NGAL proved to be a good predictor of impending AKI, its levels being 4 to 6 times more than the controls. The rise in uNGAL occurs 48 hours before the rise in serum creatinine levels. uNGAL levels were higher in children with sepsis than those without sepsis. However the relationship with AKI was maintained.

Table 2 : Laboratory Values in Acute Kidney Injury

	Prerenal	Intrinsic Renal
FENa, per cent*	< 1	> 1
BUN to creatinine ratio	> 20:1	10 to 20:1
Urine specific gravity	> 1.020	1.010 to 1.020
Urine osmolality, mOsm per kg	> 500	300 to 500
Urine sodium concentration, mEq per L (mmol per L)	< 10 (10)	> 20 (20)
Urine sediment	Hyaline casts	Granular casts

FENa = fractional excretion of sodium; BUN = blood urea nitrogen.

*-FENa is calculated as follows:

$$\text{FENa} = \frac{\text{Urine sodium} \div \text{plasma sodium}}{\text{Urine creatinine} \div \text{plasma creatinine}} \times 100$$

note: A prerenal FENa of greater than 1 per cent can occur in patients receiving chronic diuretic therapy or in patients with acute renal failure superimposed on chronic renal failure. Conversely, an intrarenal FENa of less than 1 per cent can occur with radiocontrast nephropathy and rhabdomyolysis

Approach to AKI

Before instituting measures to treat AKI it is important to identify

- whether the AKI is really acute or masking a chronic kidney disease, History of diabetes mellitus, hypertension, glomerulonephritis or kidney disease, ultrasonographically small contracted kidneys, urinalysis with broad casts-more than 2 to 3 whiteblood cells in diameter, low carbamylated hemoglobin suggest presence of chronic kidney disease.
- whether the AKI is prerenal, renal or post renal?

The priorities in treating AKI are to optimize fluid balance, treat underlying causes and institute RRT at the appropriate time.

Non Dialytic Therapy

Non-dialytic interventions in the management of AKI include restoration of euvolemic status with

crystalloid or colloids and correcting the metabolic derangements.

Pharmacological interventions with dopamine, fenoldopam. Thyroxine, Insulin like growth factor-1, loop diuretics, atrial natriuretic peptide have been found to be promising in animal studies but have failed to make a statistically significant impact in human studies. The poor results may be linked to the time interval between occurrence of AKI and the intervention .

The results of the metaanalysis of the role of loop diuretics show that frusemide has no clinical benefit in the prevention or treatment of established AKI. Its use may increase the risk of ototoxicity.⁸

The use of dopamine is associated with impaired splanchnic perfusion, increased risk of gram-negative bacteremia and an increased incidence of arrhythmias, particularly atrial fibrillation in the post open-heart patients. Hence there is no role for dopamine in the treatment of AKI.⁹

Medical management includes tight control of blood sugars besides close monitoring of the volume status, renal biochemical parameters and electrolytes. Proteinkinase C is a useful agent in systemic inflammatory reaction syndrome (SIRS) induced ARF in ICU. The backbone of treatment of ARF remains adequate supportive care, maintenance of renal perfusion pressure (MAP > 80 mm Hg), avoidance of future nephrotoxic insults and provision of renal replacement therapy.

Emerging pharmacological agents for treatment of AKI are antiapoptotic and antinecrotic agents (caspase inhibitors – nonselective and selective against Caspase 1, 3, and 7, PARP inhibitors, minocycline); anti-inflammatory (IL-10, activated protein Kinase C, iNOS inhibitor), antisepsis agents (insulin, activated protein kinase C), growth factors (recombinant erythropoietin, hepatocyte growth factor) and vasodilators (Endothelin antagonists, ANP).¹⁰

Dialytic therapy

Dialysis is one of the cornerstones of AKI treatment. Initiation of renal replacement therapy (RRT) is recommended when severe derangements in electrolyte concentration (potassium, sodium), volume overload, acid base imbalance, pronounced azotemia (BUN more than 100 mg/dl), florid symptoms of uremia (pericarditis, encephalopathy, bleeding, nausea-vomiting) are noted. Options available are peritoneal dialysis (PD), intermittent hemodialysis (IHD) extended daily dialysis (EDD), slow low efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT). PD is less preferred due to poor delivery of dialysis dose and difficulty in managing ultra filtration. However some trials have shown that continuous peritoneal dialysis has given better results in reducing morbidity and mortality in ICU ARF and is less injurious to ischemic kidney. IHD has proved to be beneficial in many of the controlled trials inspite of the fact that it may aggravate the renal injury due to fall in blood pressure. Use of more biocompatible membranes such as polysulfones or polyacrylonitrile improves the outcome of AKI by decreasing complement activation and production of leukotrienes and other cytokines.

With AKI better defined, a recognizable at risk group evolving novel biomarkers to identify AKI early, IHD itself proving to be effective dialytic mode, AKI should become a less morbid condition in the near future. However Patients who had recovered from AKI must be advised to have regular periodical follow up.

In situations of hypovolemia, hypotension and multiorgan failure (MOF) CRRT is preferred.

Role of CRRT : CRRT has potential benefits by an increased hemodynamic tolerance of dialysis, improved ability to manage fluid and electrolyte balance, improved dialytic dose delivery and use of synthetic (more biocompatible) membranes. It maintains consistent homeostasis through slow gradual shifts in volume status and serum osmolality and permits continuous control of fluid balance. There is lesser need for escalation of vasopressor

therapy and lower incidence of arrhythmias. It reduces need to restrict fluid administration, requires a lower volume of blood to be circulating outside the bag, has less effect on complements or leukocytes and has greater clearance of mid molecular weight solutes. CAVH (continuous arteriovenous hemofiltration), CAVHD (continuous arteriovenous hemodialysis), CAVHDF (continuous arteriovenous hemodiafiltration), CVVH (continuous venovenous hemofiltration), CVVHD (Continuous venovenous hemodialysis), CVVHDF (Continuous venovenous hemodiafiltration) SCUF (slow continuous ultrafiltration) are different modes of CRRT. No particular form of CRRT has yet been shown as a superior option.

In spite of the advantages of CRRT, IHD remains a more practical option (except in select clinical situations of hemodynamically unstable ARF patients) in our Indian scenario considering the additional costs involved in CRRT.¹¹

Acute Renal Failure is better termed as Acute kidney injury. The consensus definition of AKI, consensus criteria for classifying AKI and formation of AKIN will enable meaningful interpretation of data available and concrete prospective studies to lay down evidence based recommendations in the management strategies. Identification of the risk group and use of the novel biomarkers to detect early AKI will assist prevention of AKI, institution of measures to reverse AKI to normal. This will enable us to reduce the high morbidity and mortality existing in AKI. Greater awareness and preventive management per se will ensure reduction in incidence of CIN and AKI. Early Initiation of RRT will assist complete recovery. IHD is an acceptable mode of RRT among various RRT available. In select patients of AKI in ICU who are suffering from SIRS and hemodynamically unstable, CRRT will be the treatment of choice.

References

1. Molitoris BA, Levin A, Warnock DJ, Joannidis M, Mehta RL, Kellum JA, et al. Improving outcomes of acute kidney injury: report of an initiative; *Nature clinical practice Nephrology* 2007 Aug ;3 (8): 439-42.

2. LeeVWS, Harris D, Anderson J,Schrier RW. Acute Renal Failure in Robert W. Schrier, editor. Diseases of the Kidney and Urinary Tract. 8th ed. Lippincott Williams and Wilkins;2007. p 986-1025.
3. Drumi W.Acute Renal failure is not a 'cute' renal failure. *Intensive care medicine* 2004 october;30(10) 1886-90.
4. Andreoli P. Are children with a history of acute kidney Injury at risk of later Kidney Disease? *Nature clinical practice Nephrology* 2006 2: 439-42.
5. Erley C. Concomitant drugs with exposure to contrast media. *Kidney Int* 2006; 69 : S20- 22.
6. Solomon R, Bigouri C, Bettmann N. Selection of Contrast media. *Kidney Int* 2006; 69 : S39- 45.
7. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Kelly C et al. Neutrophil gelatinase associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005; 365: 1231-8
8. Ho KM, Sheriden DJ. Metaanalysis of frusemide to prevent or treat acute renal failure. *BMJ* 2006; 333:420-425.
9. Freidrick JO, AdhikariN,Herridge MS, Beyrere J. Low dose Dopamine Ineffective for Acute Kidney Failure. *Ann. Internal Med.*2005;142: 510-24.
10. Jo SK, Rosner MH, Okusa MD. Pharmacological treatment of Acute Kidney Injury: Why Drugs Haven't Worked and What is On the Horizon. *Clin J Am Soc Nephrol* 2007;2: 356-65
11. Vinsonneau C,Camus C,Combes A,Costa DE, Beauregard MA, Klouche MA, BoulaisT et al. Continuous Venovenous hemodiafiltration Versus Intermittent Hemodialysis for Acute renal failure patients with Multiorgan dysfunction Syndrome- a multicentric randomized trial. *Lancet* 2006; 368: 329-85.