ABSTRACT

The high frequency of occurrence: 5to7% in hospitalized patients, multiple clinical settings: community acquired/ hospital acquired, a high mortality and significant morbidity, requires a logical approach to the management of Acute Kidney Injury. It is important to prevent even the mildest forms of Acute Kidney Injury. The goals are to preserve renal function, to prevent complications, to avoid Renal Replacement Therapy and if possible to prevent death. In India and other developing countries, the most common causes of AKI are potentially reversible – pre-renal, pregnancy related, sepsis associated, malarial or nephrotoxic. Despite many advances in medical technology, the mortality and morbidity of AKI in ICU continue to remain high and have not improved significantly over the past 2 decades. Primary strategies to prevent ARF still include adequate hydration, maintenance of mean arterial pressure, and minimizing nephrotoxin exposure. Diuretics and dopamine have been proved to be ineffective. Increasing insight into mechanisms involved and the importance of facilitating renal recovery has led to development of newer biomarkers, which may result in a dramatic improvement in outcome of AKI. In India the renal replacement therapies are neither accessible nor affordable to vast majority of population. Early recognition and effective interventions of reversible factors is the only realistic way to decrease its impact on morbidity and mortality. The efficacy of a number of pharmacologic interventions has been evaluated in the early management of AKI.

BACKGROUND/ INTRODUCTION

Acute Kidney Injury (AKI), earlier known as Acute Renal Failure (ARF), is an acute and often reversible loss of kidney functions, irrespective of cause and mechanism. The Acute Dialysis Quality Initiative (ADQI) categorized the whole severity range of AKI into 3 severity grades and 2 outcome classes: Risk→ Injury→ Failure→ Loss→ ESRD (RIFLE) criteria. More recently system and proposed a uniform standard for diagnosing and staging AKI. The Acute Kidney Injury Network (AKIN) modified the RIFLE staging has provided the following diagnostic criteria for AKI: An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of either ≥ 26.4µmol/L or a percentage increase ≥ 50% (1.5 fold from baseline) or a reduction in urine output (documented oliguria of <0.5 mL/kg/h for > 6 hours).

LOGICAL APPROACH AND OUTCOME MEASURES:

It is important to have a rationale initiative to manage AKI as under:

1. Community vis-à-vis Hospital Acquired AKI:
   In developing countries like India, AKI is mostly community acquired, occurring in young, otherwise healthy people, secondary to tropical infections, more severe in nature yet as many as 90%, being potentially reversible. In developed nations AKI is almost hospital-acquired occurring in an ICU setting.

2. Pre-renal, Intrinsic and Post renal AKI:
   AKI may be classified on patho-physiological basis into general categories, as follows (Table.1):
   I. Pre-renal: An adaptive response to severe volume depletion and hypotension, with normal tubular and glomerular function; with structurally intact nephrons.
   II. Intrinsic: With structural and functional damage, in response to ischemic, cytotoxic, or inflammatory insults. Ischemic renal injury is the most common cause of intrinsic renal failure.
   III. Post-renal: There is an increase in tubular pressure, from obstruction to the passage of urine, decreasing the filtration driving force.

3. Oliguric Vis-à-vis Non-oliguric AKI:
   Classifying AKI as oliguric or non-oliguric based on daily urine excretion has prognostic value. Non-oliguric AKI usually occurs in hospital set-up, secondary to Nephrotoxic agents. Non-oliguric renal failure has been shown to have a better prognosis than oliguric one.

4. ICU vs. Non-ICU AKI:
   Non-ICU AKI, in which the kidney is usually the only failed organ, carries a mortality rate of up to 10%. In contrast, ICU AKI is often associated with sepsis and with non-renal
multi-organ system failure), with mortality rates of over 50%.

5. Volume-responsive vs. Volume non-responsive AKI

Volume-responsive AKI describes a functional impairment that is reversible by fluid administration. Hypovolemia is the most important cause of volume-responsive AKI. The patients with volume-responsive AKI, may be managed in non-ICU setting and may not require invasive hemodynamic monitoring.

TOP FIVE CAUSES OF AKI IN INDIA

1. Diarrhoeal diseases
2. Sepsis: Pregnancy related septicemia
3. Acute Malaria- Pfalciparum
4. Drug induced
5. Hospital Acquired

AKI IN GASTROENTERITIS:

Volume depletion due to diarrhoeal diseases is the commonest cause of AKI in India, which develops earlier and more severe in younger patients than adults. Gastroenteritis is mainly caused by rotaviruses, E.coli, H.jejuni, Shigella sps, Salmonella enteritides, Vibrio cholera, which are endemic in India, Bangladesh, Thailand and Mayanmar. Long back Chugh et al reported that in India, 63% of AKI were secondary to medical diseases, mostly due to gastrointestinal infections. The use of oral rehydration therapy, better sanitation, and availability of better health care services has led to decline in incidence of post-diarrhoeal AKI from 23% to less than 10% in last two decades.

AKI IN SEPSIS:

Sepsis affects 40% of critically ill patients. The development of kidney injury is a high predictor of mortality in sepsis, independent of initial serum creatinine levels. Older patients, hypertension, a higher APACHE score, a more severe degree of anemia, hyperalbuminemia, hyperphosphatemia and hyperkalemia were associated with a higher mortality rate.

In Pregnancy-related, acute kidney injury (PR-AKI) Septic abortion is the most common cause (~20%) of AKI in early pregnancy, whereas puerperal sepsis is the most common cause in the post partum period.

AKI IN MALARIA:

The worldwide incidence of malaria has increased, so are the complications of severe falciparum malaria. In the areas of endemic malaria, the incidence of AKI may be >4%, with mortality rate of 45% at 4-7 days. AKI in falciparum Malaria is mediated through several mechanisms. Black water fever is occasionally associated with acute renal failure. Early intervention, including appropriate anti-malarial treatment and renal replacement therapy, is associated with improved survival and recovery of kidney function.

4. Nephrotoxic Drug Induced AKI:

High risk combinations for AKI:

1. Volume depleted state AND aminoglycosides, amphotericin, diuretics, heme pigments, or radiologic contrast agents
2. Pre-existing renal disease or bilateral renal arterial disease, AND angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), Aminoglycosides
3. Hypertension, Diabetes, CHF, elderly, jaundiced patients AND NSAIDs, radio-contrast agents, aminoglycosides
4. Angiotensin-converting enzyme (ACE) inhibitors AND diuretics, bilateral renal artery stenosis

Pathophysiology of Reversible AKI:

The kidneys are probably the only organs of body, with the remarkable capacity to recover from almost total loss of function, therefore most of AKI are potentially reversible, with effective and early intervention. Regardless of the cause of ARF, reductions in RBF represent a common pathologic pathway for decreasing GFR. Recovery from ARF is first dependent upon restoration of RBF. Early RBF normalization predicts better prognosis for recovery of renal function.

ROLE OF BIOMARKERS

Early detection of AKI

The treatment of AKI ideally should begin before the diagnosis is firmly established. A high index of suspicion often is necessary to diagnose early AKI. The determination of Serum creatinine and FE Na using spot urine remains the primary and most readily available early marker of AKI.

Serum creatinine:

Serum creatinine and urine output are still considered as the best existing, most widely used, easily available and cheap markers to diagnose AKI in its relatively early stages.

Fractional excretion of sodium (FeNa):

Increase in FeNa is noted, even before oliguric phase is established and patient is still in potentially reversible phase of AKI. Cystatin-C

Cystatin-C is an endogenous cysteine proteinase inhibitor of low molecular weight. Cystatin-C is neither secreted nor reabsorbed but completely metabolized, by proximal renal tubular cells, unaffected by sex, age, height, weight, and muscle mass. Serum cystatin C has been shown superior to serum creatinine, as a
**Table-I: Potentially Reversible Causes of AKI:**

1. Renal Hypoperfusion: Shock/PCF: Hypovolemic: Diarrhoeal diseases, Malaria, Peritonitis, Leptospirosis
   - Septicemic: Burns, Pancreatitis, Septic Abortion, Post Partum, Hospital acquired, ICU setup
   - Cardiogenic: Extensive MI, CHF, Pericardial Tamponade, Anti-hypertensives
2. Renal Vasconstriction: Nephrotoxic Drugs: NSAIDS, Cyclosporin, Tacrolimus, Radiocontrast, Amphotericin
   - Hepatorenal Syndrome
3. Decreased Intra-glomerular pressure: ACE Inhibitors, ARB’s, Renin Inhibitors
4. Acute Interstitial Nephritis: Acute Pyelonephritis; Drug induced, Acute Interstitial Nephritis
5. POST- RENAL: Management Issues for Reversible factors in AKI
   - Early and Effective Intervention is The KEY:
   - Several studies of AKI suggest that up to 30% of cases may be preventable, with a significant percentage potentially reversible through simple interventions such as volume repletion, discontinuing and/or avoiding certain potentially nephrotoxic agents, and earlier recognition of conditions causing rapid progression of AKI[21]

**Kidney Injury Molecule-1 (KIM-1)**

KIM-1 is a type I trans-membrane served as a marker of severity of AKI and can be used to predict adverse outcomes in hospitalized patients better than conventionally used severity markers[22-24].

**Neutrophil gelatinase-associated lipocalin (NGAL):**

Early results suggested NGAL may be an early and sensitive urinary biomarker of sepsis-related, ischemic and nephrotoxic AKI. Another study found NGAL to represent an early biomarker of contrast-induced nephropathy with good correlation with cystatin C, serum creatinine and e-GFR in patients with normal serum creatinine undergoing coronary angiography[25].

**MANAGEMENT OF VOLUME-DEPLETION (WITH OR WITHOUT RENAL HYPOPERFUSION):**

Hypovolemia potentiates and exacerbates all forms of AKI. Correction of any volume deficit will minimize further extension of the kidney injury, and will potentially facilitate recovery from AKI.

1. Optimise volume status:
   a. CVP >10cm of water
   b. PCWP ~ 10-12 mm Hg
   c. MAP > 80 mm Hg
   d. Urine Vol. > 40 ml/hr.
2. Fluid Replacement Prescription:

   **High risk**
   - Volume Responsive AKI
   - Euvolemia

   **Volume Unresponsive AKI**
   - Hypovolemia
   - Hypervolemia
   - Euvolemia

**Therapeutic Window**

**Sensitive Biomarkers Traditional Biomarkers**

**Mortality**

Fig. 2: Narrow Therapeutic Window for Reversible AKI

The nature and the rate of fluid replacement must be guided by clinical assessment with consideration for safety limits.

3. Types of fluid:
   a. 0.9% NaCl Vs 0.45% NaCl + 5-D
   b. Crystalloid Vs Colloid

Isotonic IV fluids are indicated for the prevention of contrast-induced nephropathy and possibly for prevention of other forms of nephrotoxic ARF. The optimal composition of this fluid, beyond being isotonic, is controversial but colloids do not appear to offer any advantage[26].

Mannitol should be used with great caution, if at all, since it may result in a hyperosmolar state particular when renal failure has already occurred. The role of colloids compared to crystalloids remains unclear. ADQI Consensus: Colloids do not appear to offer any advantage over crystalloids for the prevention of ARF in critically ill patients[34-35].

**MAINTAINING RENAL PERFUSION PRESSURE:**

**Role of Vasopressors:**

Preservation of renal perfusion by support of cardiac output, mean arterial pressure and intravascular volume is recommended to facilitate renal recovery. In addition to fluid resuscitation, vasopressor agents are used to manage shock. First, nor-epinephrine and dopamine are excellent first line α-adrenergic agents (vasopressors) of similar efficacy and lesser degree of β-adrenergic activity (inotropes). In sepsis-associated AKI, small and uncontrolled studies have shown that vasopressors can improve glomerular filtration[46].

**SUPPORTIVE TREATMENT AND OTHER THERAPEUTIC STRATEGIES:**

A. Strategies of proven efficacy:
   1. Early and Effective Hydration (discussed above)
   2. Adequate Renal perfusion
3. Avoidance of Nephrotoxins
4. Drug modification; Use Non-ionic low osmolar contrast Liposomal Amphotericin

B. Strategies of probable efficacy:

1. Osmotic Diuretics: Mannitol:
   Infusion of mannitol is reported to be protective of myoglobinuric AKI, if given within 6 hours of rhabdomyolysis. Several small RCTs have found no reduction in the incidence of AKI with mannitol over hydration alone.43

2. Atrial Natriuretic Peptides (ANP), Brain Natriuretic Peptide (BNP):
   Studies with ANP suggest harm in non-oliguric patients44. There is increasing use of b-type natriuretic peptide (BNP) for treatment of refractory congestive heart failure. BNP induces natriuresis, often when other therapies are ineffective45. Although BNP appears to inhibit the renin-angiotensin system, and may therefore have effects in CHF, beyond diuresis, its effects are unproven46-48.

3. Dopamine-α1-receptor agonist Fenoldopam:
   Fenoldopam is a potent selective post-synaptic dopamine A-1 receptor agonist, small prospective studies suggest a potential benefit in terms of renal perfusion and reduction in serum creatinine with Fenoldopam.49

4. N-acetylcysteine(NAC):
   The use of N-acetylcysteine (NAC) has been shown in several trials to decrease the incidence of contrast nephropathy. However, NAC has not been shown to improve survival or need for dialysis50-52.

C. Strategies that are not effective:

1. Loop diuretics: (Furosemide, Torsemide)
   To convert oliguric AKI into non-oliguric AKI, which have better renal recovery rates, many recommend diuretics in it. Unfortunately, randomized double-blind controlled trials fail to show any benefit.44

2. Low – dose Dopamine
   Renal-dose (“low dose”) dopamine, once widely used, is ineffective in improving kidney function in AKI, overwhelming evidence exists to suggest that there is no role for “low-dose” dopamine in the prevention of ARF from any etiology.53-55

3. Adenosine agonists; Theophylline:
   Current evidence does not support a role for theophylline in the prevention of AKI.56-58

CONCLUSION
As with most disease conditions, the earlier an intervention can be instituted in Acute Kidney Injury, the more favourable the outcome. Thus, biomarkers more sensitive than the rise in serum creatinine, will be necessary to achieve early intervention.. Presently, however, the determination of FE creatinine and Cystatin-C are the most readily available early marker of established AKI. Adequate hydration, maintenance of mean arterial pressure, and minimizing nephrotoxin exposure still remain the most effective non-pharmacologic strategies to prevent AKI. There is now convincing evidence that diuretics, dopamine agonists, and natriuretic peptides do not prevent or improve outcomes once AKI is established. The role of prophylactic use of dialysis to prevent contrast nephropathy is unproven.

REFERENCES