Prevention and Management of Acute Kidney Injury: What a Physician Should Know

Danish Kathuria1, NP Singh2

Abstract
The incidence of acute kidney injury (AKI) has been increasing worldwide. The increase is attributable not only to ageing population with multiple comorbidities, polypharmacy, increasing use of contrast for diagnostic and therapeutic procedures but also to the fact that now it is being recognized more often. The ‘Zero by 25’ initiative by International Society of Nephrology aims at preventing all avoidable deaths from AKI worldwide by the year 2025. It calls for greater awareness about management of AKI among primary care physicians. In last few years, various concepts have emerged regarding prevention and management of AKI. This review aims at consolidating and applying these concepts to the ‘5R approach’ for management of AKI introduced by Lewington.

Introduction
Acute kidney injury (AKI) is an abrupt decrease in renal function irrespective of the underlying etiology. Various guidelines (RIFLE, AKIN) have attempted to define and stage AKI. These efforts have been further refined by KDIGO in 2012.1 Even slight changes in the serum creatinine have been labelled as AKI as these seemingly small changes also affect the outcome adversely.

Epidemiology and Outcome
AKI can be broadly classified into Community Acquired AKI (CA-AKI) and Hospital Acquired AKI (HA-AKI). As evident from the names, CA-AKI represents the patients who have AKI at the time of admission and HA-AKI refers to the patients who develop AKI during the course of their hospitalization. Out of the two, CA-AKI is lesser studied, underestimated (ascertainment bias), associated with more severe AKI but with similar outcome (progression to de novo chronic kidney disease and mortality) as compared to HA-AKI.3,5

Definition and Staging
AKI is defined as an increase in serum creatinine (S.Cr) by more than or equal to 0.3 mg/dl (≥26.5 μmol/l) within 48 hours or increase in S.Cr by at least 1.5 times the baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume less than 0.5 ml/kg/hour for at least 6 hours.

Small fluctuations in serum creatinine have been included in the spectrum of AKI as they have an adverse effect on the overall outcome of the patient. Moreover, it helps in early recognition of AKI and prompts early management so as to prevent its progression to more severe and irreversible forms of renal injury. But at the same time, it has added to the financial burden of healthcare and poses a great challenge to the already under resourced regions of the world.

Table 1: Staging of AKI

<table>
<thead>
<tr>
<th>AKI stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 to 1.9 times baseline or ≥ 0.3 mg/dl increase</td>
<td>&lt;0.5ml/Kg/hour for 6-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0 to 2.9 times baseline</td>
<td>&lt;0.5ml/Kg/hour for ≥ 12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3 times baseline or increase in serum creatinine to ≥ 4 mg/dl or initiation of RRT or in patients &lt; 18 years a decrease in eGFR to &lt; 35ml/min/1.73 m²</td>
<td>&lt;0.3ml/Kg/hour for ≥24 hours or anuria for ≥ 12 hours</td>
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The ‘Zero by 25’ initiative2 by International Society of Nephrology cannot be translated into reality without raising awareness among the healthcare providers. The 5R approach, proposed by Lewington et al, is an effective tool that can specifically guide physicians and allied personnel in early recognition and management of AKI.3

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Pathophysiology

A good understanding of the processes underlying AKI is essential to comprehend and embrace the concepts of its management. The major driving force for glomerular filtration comes from renal arterial blood pressure. As the renal perfusion declines due to any cause, kidneys try to maintain the glomerular capillary pressure via afferent arteriolar vasodilation and efferent arteriolar vasoconstriction— the autoregulation. So apart from causes of renal hypoperfusion, anything that impairs renal autoregulation will also result in fall in GFR (Figure 1).8

As evident in the Figure 2, afferent arteriolar vasodilatation will be impaired by NSAIDS, atherosclerotic changes in the renal arteriole and sepsis. Similarly, vasoconstriction of the efferent arteriole will be hampered by angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Prevention and Management

The 5 R Approach proposed by Lewington et al., is an effective model for prevention and management of AKI. The different components of this approach (risk assessment, recognition, response, renal support and rehabilitation) coincide with various points of contact in the healthcare system (Figure 3).

Risk Assessment

A knowledge of risk factors and susceptibilities is sufficient to identify patients at risk of developing AKI (Table 2).

Recognition

Patient at the risk of developing AKI should be closely monitored. A strict input-output charting and serial serum creatinine testing is

concluded that the most common cause of AKI in the high and middle income countries was sepsis and hypotension, while in low income countries dehydration still remains the most common cause of AKI.2 However, over the last few decades, not only the terminology of AKI (earlier acute renal failure) has changed, but also the epidemiology of AKI has evolved. In developing countries, some causes (such as diarrhea and septic abortion) are becoming less prevalent while other causes (like sepsis, nephrotoxic drugs, contrast use, HIV infection and use of antiretroviral drugs) are contributing more and more to the common etiologies of AKI.6 According to the multinational AKI-EPI study, more than half of the patients admitted in the critical care units developed some degree of acute kidney injury and there was little variation in AKI occurrence and mortality between different regions in the world.7

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must. Any patient with abrupt rise in serum creatinine and/or decreased urine output fulfilling the criteria for AKI (KDIGO, 2012) should be staged according to the same guidelines (Table 1).1

Response

A. Clinical assessment: Patient should be assessed for any obvious reversible cause of AKI. Volume status can be judged clinically. USG must be done immediately if any obstruction of urine flow is suspected. In a well hydrated patient, who is hemodynamically stable and without any evidence of obstruction, intrinsic renal disease should be suspected and worked up accordingly. While in face of hemodynamic instability, sepsis is most likely and should prompt a thorough search for the focus of infection.

B. Fluid Repletion: If the patient is hypovolemic (clinical signs of dehydration, urine output <30 ml/hour, urine specific gravity>1.020), begin resuscitation with fluids, 250-500 ml/V bolus up to 2 liters in first 2 hours.9 At this point if there is no improvement, sepsis is likely and inotropes should be considered with broad spectrum antibiotic coverage. Choice of fluid: With albumin offering conflicting results and hydroxyl-ethyl starch (HES) being associated with increased mortality and requirement for renal replacement therapy (RRT), crystalloids remain the preferred fluids. Among crystalloids, normal saline is associated with hyperchloremic acidosis which itself can cause arteriolar vasoconstriction resulting in reduced GFR. Hence, a more balanced low chloride fluid like Ringer’s lactate solution may be a better option.9

C. Watch for fluid overload: Role of diuretics: In critically ill patients, with some degree of tubular damage already set in, patients may begin to accumulate fluid (Figure 4) and at this time a diuretic challenge would be appropriate. The 2-hour urine output less than 200ml after a standardized high-dose furosemide stress test (FST, 1mg/kg of furosemide in naive patients or 1.5 mg/kg in those with prior exposure to furosemide) in clinically euvoletic patients with early AKI, predicts progression to more severe forms of AKI.10 However, when used to treat AKI, loop diuretics may increase mortality in patients with critical illness and AKI.11 Hence, loop diuretics should be used neither to prevent nor to treat AKI unless there is fluid overload.

D. Role of inotropes: Systolic blood pressure (SBP) is the major determinant of net filtration pressure. The next best step in hypotensive but fluid replete patient is initiation of inotropes. The inotropes should be titrated to a target mean arterial pressure (MAP) of 65 mm Hg. Noradrenaline remains the inotrope of choice. Dobutamine is best avoided as it causes vasodilation further worsening renal perfusion. There is no role of much hyped ‘renal dose’ of dopamine.8

E. Review of medications: Following salient points should be kept in mind while managing a patient with AKI:

1. All medications should be administered as per estimated GFR (eGFR), specially the renally eliminated antibiotics.

2. Drugs interfering with autoregulation should be avoided: NSAIDS, ACE-inhibitors, Angiotensin receptor blockers etc.

3. Drugs known to cause hyperkalemia should be avoided: potassium sparing diuretics, beta blockers, digoxin, trimethoprim etc.

F. Glycemic Control: Hyperglycemia (Blood glucose > 180 mg/dl) has been associated with increased mortality among patients with AKI. Though intensified insulin therapy achieving tight control (80-110 mg/dl) is associated with favorable renal outcomes, but it increases the risk of hypoglycemia. Thus, the KDIGO working group
Table 3: Daily recommended intake for patients with AKI

<table>
<thead>
<tr>
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<th>Not on RRT</th>
<th>On RRT</th>
<th>On CRRT</th>
</tr>
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<tbody>
<tr>
<td>Total Energy</td>
<td>20-30 Kcal/Kg body weight(BW)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>3-5 g/Kg BW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fats</td>
<td>0.8-1g/Kg BW</td>
<td>1-1.5g/Kg BW</td>
<td>1.7g/Kg BW</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.8-1g/Kg BW</td>
<td>1.5g/Kg BW</td>
<td>1.7g/Kg BW</td>
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G. Nutritional support: The deranged metabolism and inflammation due to primary pathology underlying the renal dysfunction, requires special nutritional considerations. Table 3 sums up the nutritional recommendations by the KDIGO guidelines.

Renal Support

Knowing when to call for help and a timely referral to the nephrologist is important. While the absolute indications for dialysis are well known (refractory fluid overload, metabolic acidosis, hyperkalemia and uremic complications), renal support (in the form of RRT) provides the body with a chance and time to recover from the underlying disease.

The optimal timing of renal support is still a matter of debate. According to the KDIGO review, delayed RRT was associated with increased mortality, longer duration of hospital stay and dependency on RRT. This was further supported by the ELAIN trial, which reported reduced mortality at 3 months with early RRT (within 8 hours of diagnosis of KDIGO stage 2 AKI) as compared to delayed RRT (within 12 hours of diagnosis of stage 3 AKI). However, a more recent meta-analysis and systematic review by Xu et al., concluded that early RRT has no impact on the renal outcome.

Options include continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD) or slow low efficiency hemodialysis (SLED). The details of different modalities of RRT is beyond the scope of this article, however as recommended by the KDIGO guidelines CRRT, rather than standard intermittent RRT, is preferred for hemodynamically unstable patients. In such patients, SLED is logistically more viable option, when CRRT is either not available or not affordable. However in primary health care centers where modes of extra corporeal hemofiltration (CRRT, IHD and SLED) are not available, peritoneal dialysis is still widely used. Apart from being affordable, it is simpler and equally effective method of renal replacement, especially in young patients without multi-organ dysfunction and multiple comorbidities.

RRT should be discontinued as soon as it is no longer required, i.e. when intrinsic kidney function has recovered to the point that it is adequate to meet patient needs.

Rehabilitation

AKI has been linked to the development of de novo CKD as well as progression of already existing CKD. Hence, a regular follow up with both the physician as well as the nephrologist is essential for early detection of CKD and its management. A holistic approach by the physician by treating the comorbid conditions may not only halt the progression to CKD but will also improve the quality of life.

AKI in Special Situations

Contrast induced acute kidney Injury (CI-AKI): CI-AKI is abrupt deterioration in renal function following contrast use e.g. for coronary angiography, contrast enhanced imaging studies etc. It is defined and staged according to the same criteria used for other forms of AKI. Vulnerable patients include elderly (age >75years), diabetics, ones with hypotension, pre-existing renal impairment (estimated GFR<60ml/min/1.73 m²), advanced heart failure and anemia. Procedures involving contrast media should be best avoided in such patients. After carefully weighing risks and benefits of the procedure, if it still needs to be done, pre procedure hydration is the most effective intervention to prevent CI-AKI. Other strategies for prevention of CI-AKI include using low osmolar contrast media in minimal possible amount and use of oral N-acetyl cysteine.

Post cardiothoracic surgery AKI: AKI following a major cardiac surgery is a well-known entity and according to a study by Hobson et al., AKI complicates about 37% of coronary, 49% of valvular and 55% of aortic surgeries. More importantly, it is associated with increased long term risk of end stage renal disease- as high as 3-times in patients with AKI following coronary artery bypass grafting (CABG). The most important pathophysiological factor contributing to renal insufficiency in such patients is intra-operative hypotension and renal hypoperfusion. The use of cardiopulmonary bypass (CBP) also plays a role in pathogenesis by activation of inflammatory cascade and alterations in coagulation. Among all the strategies studied (including vasodilators, antioxidants etc.), pre procedure hydration is the most effective strategy for preventing AKI in this subset of patients.

Drug induced AKI: There is a huge list of drugs which can result in renal impairment. The most common ones are the non-opioid analgesics, antimicrobial agents (aminoglycosides, vancomycin, amphotericin B) and...
chemotherapeutic agents. The essence of preventing drug-induced AKI is using these drugs only when absolutely indicated and when no other alternatives are available, using the right dose as per the estimated GFR, monitoring renal function closely and withdrawing the drug as soon as there is renal impairment.

**Conclusion**

If recognized and appropriately managed in time, most of the morbidity and mortality from AKI is preventable. A team effort, beginning at early identification by the paramedics and the physicians, a rapid response to correct the reversible causes and a timely referral to the nephrologist form the key components of the 5 R model.

**References**