Updates in Management and Timing of Dialysis in Acute Kidney Injury

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Acute kidney injury (AKI) is a common complication in hospitalized patients and is associated with mortality, prolonged hospital length of stay, and increased healthcare costs. This paper reviews several areas of controversy in the identification and management of AKI. Serum creatinine and urine output are used to identify and stage AKI by severity. Although standardized definitions of AKI are used in research settings, these definitions do not account for individual patient factors or clinical context which are necessary components in the assessment of AKI. After treatment of reversible causes of AKI, patients with AKI should receive adequate volume resuscitation with crystalloid solutions. Balanced crystalloid solutions generally prevent severe hyperchloremia and could potentially reduce the risk of AKI, but additional studies are needed to demonstrate a clinical benefit. Intravenous albumin may be beneficial in patients with chronic liver disease either to prevent or attenuate the severity of AKI; otherwise, the use of albumin or other colloids (eg, hydroxyethyl starch) is not recommended. Diuretics should be used to treat volume overload, but they do not facilitate AKI recovery or reduce mortality. Nutrition consultation may be helpful to ensure that patients receive adequate, but not excessive, dietary protein intake, as the latter can lead to azotemia and electrolyte disturbances disproportionate to the patient’s kidney failure. The optimal timing of dialysis initiation in AKI remains controversial, with conflicting results from two randomized controlled trials. Journal of Hospital Medicine 2019;14:232-238. Published online first February 20, 2019. © 2019 Society of Hospital Medicine

DEFINITION OF ACUTE KIDNEY INJURY

AKI refers to an acute change in kidney function characterized by an increase in serum creatinine and/or a reduction in urine output. It is a clinical syndrome caused by a broad range of etiologies and may be related to primary kidney pathology and/or systemic illness. Until 2004, there was no standard definition for AKI and over 30 different definitions were found in the literature, which resulted in wide variation in the reported incidence and outcomes of AKI and made it challenging to apply an evidence-based approach to patient care. In 2004, the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE)14 criteria for AKI were proposed, which were modified to the Acute Kidney Injury Network (AKIN)15 criteria in 2007 (Table 1). Multiple studies show that the RIFLE and AKIN criteria for AKI are associated with higher mortality12,8,10 and increased risk for requiring RRT.11

International clinical practice guidelines for AKI were released by Kidney Disease: Improving Global Outcomes (KDIGO) in 2012, which included a standardized definition of AKI that was adapted from the previously validated RIFLE and AKIN definitions.16 Patients are considered to have AKI when the serum creatinine rises by as little as 0.3 mg/dL. It is notable that when the baseline serum creatinine is high, there is more inherent variability in the serum creatinine measurement; thus, patients with CKD have a higher risk of being misclassified as having AKI.17 Although the KDIGO definition for AKI is commonly used in research settings, components of this definition have not been well validated, and it is not widely used in clinical practice. Other renal professional societies still recommend an individualized approach to the diagnosis of AKI, taking into account clinical importance, several areas of controversy remain regarding the management of AKI and, in particular, the optimal timing of renal replacement therapy (RRT) in patients with AKI. The purpose of this manuscript is to review the approaches to diagnosis and management of AKI in hospitalized patients. We also review recent evidence regarding the timing of dialysis in patients with AKI. This journal recently reviewed the differential diagnosis and diagnostic evaluation of AKI, which is not covered here.13
account other factors such as trajectories in kidney function, fluid balance, electrolyte abnormalities, comorbid conditions, and clinical context. While we endorse the KDIGO approach to the categorization of AKI severity, in practice, a more patient-centered approach is generally required to guide the optimal approach to determining the etiology of AKI and guiding management.

**GENERAL MANAGEMENT OF ACUTE KIDNEY INJURY**

All patients with AKI should have close monitoring of their serum creatinine and urine output. Noninvasive diagnostic studies (urine microscopy, postvoid residual, and renal ultrasound) should be considered based on the clinical scenario. General management strategies include treatment of the reversible causes of AKI and optimization of volume status, hemodynamics, and nutritional status (Table 2).

**Reversible Causes of Acute Kidney Injury**

The first step in the treatment of AKI is to identify and treat readily reversible causes of AKI such as volume depletion, hypotension, infection, and urinary obstruction. Nephrotoxins should be avoided and all medications should be reviewed and adjusted for kidney function, particularly those that may affect mental status. Avoid opiates with noxious or active metabolites, including meperidine and morphine. Instead, hydro-
Intravenous fluids
For most patients, albumin has an unproven benefit compared with crystalloid solutions. Hydroxyethyl starch is not recommended. Balanced crystalloid solutions reduce the risk of severe hyperchloremia and acidosis and may be associated with a lower risk of AKI.

Volume resuscitate with crystalloid solutions. Consider balanced crystalloid solutions to avoid severe hyperchloremia and acidosis in large volume (>2 L) resuscitation, particularly in critically ill patients.

Diuretics
Diuretics do not directly affect AKI recovery or survival. Patients with AKI may need high doses of diuretics to respond. Only use diuretics as needed for volume overload.

Nutrition
Patients in catabolic states may have high protein requirements. Excess protein intake may contribute to azotemia out of proportion to renal failure. Nutrition consultation is recommended to ensure adequate, but not excessive, protein intake.

Renal replacement therapy
Optimal timing of renal replacement therapy is not known. No evidence for mortality benefit of continuous renal replacement therapy over intermittent hemodialysis. Medical management of fluid and electrolyte abnormalities in nonoliguric patients with AKI should be attempted while assessing renal replacement therapy needs.
Diuretics

As above, volume status is a key component in the management of patients with AKI. In patients with AKI and hypervolemia, loop diuretics are often given prior to the initiation of RRT. Loop diuretics act on the sodium-potassium-chloride cotransporters in the thick ascending limb of the loop of Henle to increase urinary losses of these ions and urine volume. Loop diuretics are dose-dependent, and often, higher doses are needed (eg, furosemide 100 mg intravenous dose) in patients with AKI, since the diuretic effect depends on the proximal tubular secretion of the drug into the urine. The role of diuretics in AKI is controversial and some observational data suggest an increased mortality risk with diuretic use in patients with AKI. In critically ill patients with acute lung injury, diuretic use improved survival, which was attributed to better control of volume overload. But, a meta-analysis of 11 randomized controlled trials failed to demonstrate that diuretics directly improved survival or recovery of AKI. Moreover, randomized controlled trials found that diuretics given to a patient with AKI requiring RRT did not improve recovery of kidney function. The KDIGO guidelines recommend that diuretics should not be routinely used for AKI except in the management of volume overload.

Nutritional Targets in Acute Kidney Injury

Critically ill patients have high protein catabolic rates, which put them at increased risk for malnutrition, which in turn is associated with mortality. Patients who receive continuous RRT (CRRT) may lose 5-10 g of protein and 10-15 g of amino acids daily, and these patients may have protein requirements that are twice the usual recommended daily protein intake. But excess protein administration can result in high urea generation and azotemia unrelated to the patient's kidney function. Blood urea nitrogen may also be disproportionately elevated in conditions where tubular reabsorption of urea is increased, such as in volume depletion, diuretic use, corticosteroid use, and gastrointestinal bleeding. Interpretation of blood urea nitrogen results must be made in the appropriate clinical context, with recognition that azotemia alone may not be a good surrogate marker of the patient's underlying kidney function. We recommend dietary consultation in critically ill patients with AKI to ensure that adequate, but not excessive, protein is administered.

RENNAL REPLACEMENT THERAPY IN ACUTE KIDNEY INJURY

In patients with AKI, RRT is initiated for control of volume overload, electrolyte abnormalities, acidemia, or uremic symptoms or complications that are refractory to medical management (Table 3). In a nonoliguric patient, fluid and electrolyte abnormalities can oftentimes be managed medically. Patients with oligoanuria (generally defined as urine output less than 400 mL/day or <20 mL/hour), however, require nephrology evaluation for consideration of RRT. Early nephrology consultation (within 48 hours of AKI diagnosis) may be associated with lower dialysis dependence and mortality in critically ill patients with AKI. The decision to initiate dialysis is individualized based on the patient's comorbid conditions, urine output, and trajectory of kidney function.

**TABLE 3. Potential Indications for Renal Replacement Therapy and Medical Treatment Alternatives**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diuretics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume Overload</td>
<td>Diuretics</td>
<td>RRT may be considered in nonoliguric patients with pulmonary edema or severe heart failure.</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Sodium bicarbonate</td>
<td>Binding resins are avoided in patients with recent abdominal surgery.</td>
</tr>
<tr>
<td>Acidemia</td>
<td>Sodium bicarbonate</td>
<td>Generally not needed if pH &gt;7.20, but there is no consensus regarding when to start RRT for acidemia.</td>
</tr>
<tr>
<td>Uremic Symptoms or Complications</td>
<td>Not applicable</td>
<td>RRT is generally started before severe complications (pericarditis and seizures) are observed.</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.
TABLE 4. Comparison of Randomized Trials of Early Versus Late Dialysis in Patients with AKI

<table>
<thead>
<tr>
<th>Study design</th>
<th>ELAIN</th>
<th>AKIKI</th>
<th>IDEAL-ICU</th>
<th>STARRT-AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country/Setting</td>
<td>Germany</td>
<td>France</td>
<td>France</td>
<td>15 countries,</td>
</tr>
<tr>
<td></td>
<td>Single center ICU</td>
<td>31 ICUs</td>
<td>27 ICUs</td>
<td>111 ICUs</td>
</tr>
<tr>
<td>Patient population</td>
<td>231 patients with critical illness and at least stage 2 AKI</td>
<td>620 patients with critical illness and stage 3 AKI</td>
<td>864 patients with septic shock and AKI (RIFLE stage failure)</td>
<td>2,866 patients with severe AKI</td>
</tr>
<tr>
<td>Intervention</td>
<td>Early dialysis</td>
<td>Within 6 hours of stage 3 AKI</td>
<td>Within 12 hours after diagnosis of AKI</td>
<td>Within 12 hours of study eligibility</td>
</tr>
<tr>
<td>Control</td>
<td>Late dialysis</td>
<td>Standard indications for RRT</td>
<td>At least 48 hours after diagnosis of AKI</td>
<td>&gt;12 hours of study eligibility</td>
</tr>
<tr>
<td>Dialysis modality</td>
<td>Continuous venovenous hemodiafiltration</td>
<td>Provider discretion (47% intermittent RRT only)</td>
<td>Provider discretion</td>
<td>Provider discretion</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Mortality at 90 days</td>
<td>Mortality at 60 days</td>
<td>Mortality at 90 days</td>
<td>Mortality at 90 days</td>
</tr>
<tr>
<td>Results</td>
<td>20-hour difference between groups</td>
<td>55-hour difference between groups</td>
<td>To be determined</td>
<td>To be determined</td>
</tr>
<tr>
<td></td>
<td>Lower mortality in early dialysis group (HR 0.66, 95% CI 0.45-0.97)</td>
<td>No difference in mortality between groups (P = .79)</td>
<td>Greater renal recovery at 90 days, shorter duration of RRT, and shorter hospital length of stay with early dialysis</td>
<td>Greater renal recovery at 90 days, shorter duration of RRT, and shorter hospital length of stay with early dialysis</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; AKIKI, Artificial Kidney Initiation in Kidney Injury Study; ELAIN, Early vs Late Initiation of Renal Replacement Therapy in Critically Ill Patients with AKI; ICU, intensive care unit; IDEAL-ICU, Initiation of Dialysis Early Versus Delayed in ICU; RIFLE, Risk, Injury, Failure, Loss, and End-stage kidney disease; RRT, renal replacement therapy; STARRT-AKI, Standard versus Accelerated Initiation of RRT in AKI.

Timing of Renal Replacement Therapy

The optimal timing of dialysis initiation in patients with AKI is not known. Theoretically, earlier initiation of dialysis could allow for better volume and electrolyte control and prevent the development of more serious complications of kidney failure such as uremic seizures, encephalopathy, and pericarditis. However, RRT is associated with its own risks and earlier initiation may expose the patient to unnecessary procedures and complications that might delay renal recovery. A meta-analysis of predominantly observational data found that earlier initiation of RRT in AKI was associated with lower 28-day mortality, greater renal recovery, decreased duration of RRT, and decreased ICU length of stay.43 Subsequently, two prospective trials reported conflicting results regarding associations between dialysis timing and outcomes in patients with severe AKI (Table 4).44,45

The Early vs Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury (ELAIN) was a prospective, single-center randomized trial in Germany of 231 critically ill, predominantly surgical ICU patients (about half postcardiac surgery) with at least KDIGO stage 2 AKI.44 Patients were randomized to early (within eight hours of developing KDIGO stage 2 AKI) or delayed (within 12 hours of developing KDIGO stage 3 AKI) RRT initiation; patients in the early RRT group initiated dialysis on average 20 hours earlier than the patients in the late group. All patients were treated with continuous venovenous hemodiafiltration. Early RRT initiation was associated with a 34% lower risk of mortality at 90 days, shorter hospital length of stay, and shorter RRT duration compared with delayed RRT initiation. There was no difference between groups in dialysis dependence at 90 days, but there was a lower risk of dialysis dependence at one year.46

The Artificial Kidney Initiation in Kidney Injury Study (AKIKI)46 was a prospective, multicenter randomized trial in France that compared early versus delayed strategies of RRT initiation in 620 critically ill, mostly medical ICU patients with severe AKI (KDIGO stage 3). The median time between randomization and RRT initiation was two hours for the early and 57 hours for the delayed strategy groups. There were no differences between groups in length of hospital or ICU stay, vasopressor use, dialysis dependence, or 60-day survival. The early strategy group had a higher incidence of catheter-related bloodstream infections (10% vs 5%) and hypophosphatemia (22% vs 15%) compared with that of the delayed strategy group. Patients in the delayed strategy group regained normal urine output sooner than in the early strategy group. Approximately half of the patients in the delayed strategy group avoided RRT altogether. The authors of AKIKI concluded that there was no benefit to the early strategy of RRT in critically ill patients with severe AKI, and a delayed strategy of RRT initiation may avoid unnecessary RRT and reduce catheter-related infectious complications.

How can we interpret these discrepant results? Although ELAIN found a benefit to earlier RRT initiation in AKI, it has lim-
ized generalizability to medical ICU patients, who have higher mortality and whose outcomes might be less affected by dialysis timing. Patients in ELAIN had a high prevalence of congestive heart failure and CKD; it is possible that select patient populations may derive greater benefit from earlier RRT initiation. Although both ELAIN and AKIKI used the standardized criteria for RRT initiation, neither study could incorporate important clinical factors such as trajectory of kidney function, comorbid conditions, or symptoms, which play a significant role in the decision-making process in real-world clinical practice. Additional large-scale, multicenter trials are needed to guide the timing of RRT in critically ill patients with AKI. The Initiation of Dialysis Early Versus Delayed in the ICU (IDEAL-ICU) and Standard versus Accelerated Initiation of RRT in Acute Kidney Injury (STARRT-AKI) studies are currently underway and hope to provide clearer guidance regarding the optimal timing of RRT initiation in AKI (Table 4). Until further evidence is available, experts recommend taking into consideration the trajectory of kidney disease, concurrent organ dysfunction, and expected need for fluid and solute control when making decisions regarding RRT initiation in AKI.16

DIALYSIS MODALITIES IN ACUTE KIDNEY INJURY

When RRT is required in patients with AKI, the dialysis modality is often determined by local availability. CRRT and sustained low-efficiency dialysis (SLED) are thought to be better tolerated than intermittent hemodialysis in hemodynamically unstable patients, although a randomized controlled trial could not demonstrate a survival difference between these modalities.49 In general, in settings where CRRT or SLED is available, these modalities are favored for patients with hemodynamic instability, but practice patterns vary widely.

CONCLUSION

Among hospitalized patients, AKI is common and associated with a higher risk of mortality. Although serum creatinine and urine output criteria are used to define AKI, other clinical factors (comorbid conditions, volume status, and trajectory of kidney function decline) can inform the assessment and management of patients with AKI. General strategies for AKI management include treatment of reversible conditions, optimization of volume status, hemodynamics, and nutritional status. The optimal timing of RRT in critically ill patients with AKI is not known, with unclear mortality benefit of earlier dialysis initiation. Two large-scale randomized controlled trials regarding early versus delayed dialysis timing in AKI are currently underway and will hopefully provide clarity in the near future.

Disclosures: Dr. Yu and Dr. Kamal have nothing to disclose. Dr. Chertow is an advisor to DURECT Corporation, a biopharmaceutical company.

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