

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

Acute kidney injury (AKI) is a common complication in hospitalized patients, affecting one in five inpatients^{1,2} and more than half of patients in intensive care units (ICU).³ The incidence of AKI appears to be increasing over time.⁴ Potential contributing factors include an aging population, rising prevalence of comorbid conditions such as heart failure and chronic kidney disease (CKD), using nephrotoxic agents, and increasing complexity of surgical procedures.^{5,6} AKI during a hospital stay is associated with a two- to 10-fold increased risk of inhospital mortality,^{1,2,7-10} longer hospital length of stay,^{7,10} higher risk for hospital readmissions,¹¹ and higher healthcare costs.⁷ Patients who survive an episode of AKI have a higher risk for CKD and dialysis-dependence,⁹ even after an episode of reversible AKI.¹² Despite its 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

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 mortality^{1,2,8,10} and increased risk for requiring RRT.^{1,10}

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

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TABLE 1. Serum Creatinine and Urine Output Criteria for Acute Kidney Injury

	Serum Creatinine Criteria			Urine Output Criteria (Common to All)	
	RIFLE	AKIN ^b	KDIGO		
Definition	≥50% increase from baseline or GFR decline >25% over 7 days ^a			<0.5 mL/kg/hour for 6 hours	
Staging	Risk	≥50% increase or GFR decline >25%	1 Increase ≥0.3 mg/dL or ≥50% increase	1 Increase ≥0.3 mg/dL or ≥50% increase	<0.5 mL/kg/hour for 6 hours
	Injury	≥100% increase or GFR decline >50%	2 ≥100% increase	2 ≥100% increase	<0.5 mL/kg/hour for 12 hours
	Failure	≥200% increase or GFR decline >75% or sCr ≥4 mg/dL with acute rise ≥0.5 mg/dL	3 ≥200% increase or sCr ≥4 mg/dL with acute rise ≥0.5 mg/dL or RRT	3 ≥200% increase or sCr ≥4 mg/dL ^c or RRT	<0.3 mL/kg/hour for 24 hours or Anuria for 12 hours
	Loss	RRT for ≥4 weeks			
	End-stage kidney disease	RRT for ≥3 months			
Strengths	Validated criteria and staging system; higher stages are associated with higher mortality and RRT dependence	Validated criteria and staging system; higher stages are associated with higher mortality and RRT dependence Incorporates smaller changes in serum creatinine Less reliant on knowledge of baseline creatinine	Uses components of previously validated criteria from RIFLE and AKIN	Urine output may be more sensitive than serum creatinine	
Weaknesses	Creatinine-based measure is limited in certain populations (catabolic states or sarcopenia) Need to know baseline creatinine or GFR Assumption of baseline GFR results in misclassification Serum creatinine change does not correlate with GFR change from the same stage Creatinine and urine output criteria from the same stage do not have similar mortality risk	Creatinine-based measure is limited in certain populations (catabolic states or sarcopenia) Small changes in serum creatinine in patients with CKD may result in misclassification Need two separate creatinine measures within 48 hours	Creatinine-based measure is limited in certain populations (catabolic states or sarcopenia) Small changes in serum creatinine in patients with CKD may result in misclassification	Urine output criteria are less well validated than creatinine-based criteria for acute kidney injury	

^aIf baseline renal function is unknown and there is no known history of CKD, then the baseline GFR of 75 mL/min/1.73 m² is used.

^bApply diagnostic criteria after adequate fluid resuscitation. Rule out urinary tract obstruction before making the diagnosis based on urine output criteria alone.

^cMust also fulfill the creatinine-based definition of acute kidney injury (creatinine ≥0.3 mg/dL over 48 hours or ≥50% increase from baseline over 7 days).

Abbreviations: AKIN, Acute Kidney Injury Network¹⁴; CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes¹⁵; RIFLE, Risk, Injury, Failure, Loss, End-stage kidney disease¹³; RRT, renal replacement therapy; sCr, serum creatinine.

account other factors such as trajectories in kidney function, fluid balance, electrolyte abnormalities, comorbid conditions, and clinical context.^{18,19} 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-

TABLE 2. Summary of Management Considerations in Acute Kidney Injury

AKI Management	Comments	Recommendations
Identify and treat reversible causes of Acute Kidney Injury	Obtain detailed history and examination. Review all medications.	Identify and treat hypovolemia, hypotension, infection, and urinary obstruction. Avoid nephrotoxins. Renally dose medications.
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.

morphine, fentanyl, and methadone are preferred in patients with AKI. Other commonly used medications that require dose adjustment include gabapentin, baclofen, metoclopramide, H2 antagonists, many commonly prescribed antibiotics (penicillins, most cephalosporins, carbapenems, quinolones, and sulfa drugs), many hypoglycemic agents, and insulin. For patients on RRT, dosing is dependent on dialysis modality. Consultation with a hospital pharmacist is recommended when RRT modalities are initiated or changed.

Intravenous Fluids

Patients with AKI should have their volume status assessed and receive adequate resuscitation with intravenous fluids to promote renal perfusion. However, the optimal type and volume of fluid to give in AKI remains controversial. Colloid-containing solutions are theoretically confined to the intravascular space and should pose a lower risk for pulmonary edema compared with crystalloids. However, these solutions are costly, are not associated with any meaningful benefit,²⁰⁻²² and may even be associated with potential harm.²²⁻²⁷

The most commonly used colloid worldwide is hydroxyethyl starch (HES). Its potential adverse effects include anaphylactoid reactions, coagulopathy, and AKI. HES is cleared by the kidneys and can cause osmotic nephrosis, a form of AKI characterized by vacuole formation and proximal renal tubular damage.²⁸ Randomized controlled trials have shown an increased risk of AKI, RRT use, and mortality in critically ill patients who were resuscitated with HES.^{22,26,27} HES is not currently recommended in patients who are critically ill or have impaired kidney function and sepsis guidelines advise against its use.²⁹

In the United States, albumin is the most common colloid-containing solution used for intravascular volume resuscitation. Albumin has been shown to be safe for volume resuscitation

in critically ill patients,²⁰ but there is no proven advantage to using albumin over saline with respect to mortality, length of hospital stay, duration of mechanical ventilation, duration of RRT, or number of organ systems failure.^{20,21} Furthermore, albumin may be harmful in certain patient populations. In patients with traumatic brain injury, albumin resuscitation is associated with higher mean intracranial pressures²³ and long-term mortality.²⁴ In a retrospective study of patients undergoing cardiac surgery, albumin administration was associated with more than twice the risk of AKI compared with crystalloids.²⁵ In contrast, in patients with cirrhosis, intravenous albumin lowers the rate of AKI when administered in the setting of a large volume paracentesis³⁰ or spontaneous bacterial peritonitis.³¹ Outside of these narrow settings, current evidence does not support the use of intravenous albumin to prevent AKI and we would not endorse the use of intravenous albumin as a part of the treatment paradigm for established AKI.

Many renal and critical care guidelines recommend initial fluid resuscitation with isotonic crystalloids except in specific circumstances (ie, hemorrhagic shock), with consideration of albumin in select cases (ie, severe sepsis or cirrhosis).^{16,18,19,29} That stated, the optimal type of crystalloid solution that should be used in resuscitation remains unclear. Because of its low cost, normal (0.9%) saline is the most commonly used solution, but it can result in hyperchloremic metabolic acidosis, which can cause renal vasoconstriction and may be associated with mortality in critically ill patients.³² A prospective study found that administration of chloride-liberal fluids (including normal saline) to critically ill patients was associated with nearly twice the risk of AKI and RRT use compared with chloride-restrictive fluids,³³ but a subsequent trial found no difference in AKI or mortality among patients receiving saline versus a balanced crystalloid (Plasma-Lyte 148).³⁴ A recent pair of large, random-

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

	Medical Treatment Alternatives to RRT	Comments
Volume Overload	Diuretics	RRT may be considered in nonoliguric patients with pulmonary edema or severe heart failure.
Hyperkalemia	Insulin/glucose Beta 2 agonists Sodium bicarbonate Diuretics Binding resins	Binding resins are avoided in patients with recent abdominal surgery.
Acidemia	Sodium bicarbonate Balanced crystalloid solutions	Generally not needed if pH >7.20, but there is no consensus regarding when to start RRT for acidemia.
Uremic Symptoms or Complications	Not applicable	RRT is generally started before severe complications (pericarditis and seizures) are observed.

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

ized control trials compared outcomes in patients at a single center who were resuscitated with normal saline versus balanced crystalloid solutions (Lactated Ringer's or Plasma-Lyte A).^{35,36} In critically ill patients, the use of balanced crystalloid solutions was associated with a lower risk of the composite outcome of mortality, new RRT, or persistent kidney impairment, but there were no differences in any of the individual components of the composite outcome.³⁵ In noncritically ill patients, there were no differences in the number of hospital-free days based on the type of crystalloid solution used.³⁶ In the absence of compelling evidence for using balanced crystalloid solutions, we continue to use normal saline for initial fluid resuscitation, but to avoid severe hyperchloremia and acidosis, we will consider switching to a balanced solution (Lactated Ringer's, Plasma-Lyte, or Normosol) for large volume resuscitation (>2 L), particularly in critically ill patients.

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.³⁷ In critically ill patients with acute lung injury, diuretic use improved survival, which was attributed to better control of volume overload.³⁸ But, a meta-analysis of 11 randomized controlled trials failed to demonstrate that diuretics directly improved survival or recovery of AKI.³⁹ Moreover, randomized controlled trials found that diuretics given to a patient with AKI requiring RRT did not improve recovery of kidney function.^{40,41} The KDIGO guidelines recommend that diuretics should not

be routinely used for AKI except in the management of volume overload.¹⁶

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.¹⁶ 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.

RENAL 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.⁴² The decision to initiate dialysis is individualized based on the patient's comorbid conditions, urine output, and trajectory of kidney function.

TABLE 4. Comparison of Randomized Trials of Early Versus Late Dialysis in Patients with AKI

	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI
Study design	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial
Country/Setting	Germany Single center ICU	France 31 ICUs	France 27 ICUs	15 countries, 111 ICUs
Patient population	231 patients with critical illness and at least stage 2 AKI Mostly surgical ICU (47% cardiac surgery)	620 patients with critical illness and stage 3 AKI Mostly medical ICU	864 patients with septic shock and AKI (RIFLE stage failure)	2,866 patients with severe AKI
Intervention (early dialysis initiation)	Within 8 hours of stage 2 AKI	Within 6 hours of stage 3 AKI	Within 12 hours after diagnosis of AKI	Within 12 hours of study eligibility
Control (delayed dialysis initiation)	Within 12 hours of stage 3 AKI	Standard indications for RRT	At least 48 hours after diagnosis of AKI	>12 hours of study eligibility
Dialysis modality	Continuous venovenous hemodiafiltration	Provider discretion (47% intermittent RRT only)	Provider discretion	Provider discretion
Primary outcome	Mortality at 90 days	Mortality at 60 days	Mortality at 90 days	Mortality at 90 days
Results	20-hour difference between groups Lower mortality in early dialysis group (HR 0.66, 95% CI 0.45-0.97) Greater renal recovery at 90 days, shorter duration of RRT, and shorter hospital length of stay with early dialysis	55-hour difference between groups No difference in mortality between groups (P = .79) 49% of the delayed dialysis group did not get dialysis A higher rate of catheter-related bloodstream infections in the early dialysis group (10% vs 5%, P = .03)	To be determined	To be determined

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 ini-

tiation 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)⁴⁵ 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-

ited 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)⁴⁷ and Standard versus Accelerated Initiation of RRT in Acute Kidney Injury (STARRT-AKI)⁴⁸ 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.

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