Acute Renal Failure in Critically Ill Patients: Current Evidence-Based Practices

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ABSTRACT

Acute kidney injury (AKI) is a common condition amongst critically ill patients in the medical intensive care unit (ICU) and is associated with increased morbidity and mortality. There are several areas of ongoing debate regarding management of AKI, specifically the initiation and timing of renal replacement therapy (RRT). In this review, we aim to concisely discuss epidemiology, current evidence with regards to optimal vascular access, timing of initiation and modality of renal replacement therapy in acute kidney injury in critically ill patients.

KEYWORDS: acute kidney injury (AKI), critically ill, renal replacement therapy (RRT)

EPIDEMIOLOGY

AKI is defined as a sudden decrease in renal function and is conventionally diagnosed utilizing the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. KDIGO defines AKI as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours, or an increase in serum creatinine ≥1.5 times baseline, known to have occurred within the prior seven days or urine volume <0.5 mL/kg/hour for at least six hours (**Table 1**).[1] Accepted alternate criteria exist and include those proposed by the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) group and criteria posed by the Acute Kidney Injury Network (AKIN) (**Tables 1, 2**).

AKI affects up to half of medical intensive care unit patients and is associated with increased length of ICU stay, increased hospital stay, development of chronic kidney disease and increased short-term and long-term mortality.[2] In fact, more than 13% of critically ill patients will receive RRT within the first week of their ICU stay.[2] Mortality rates in critically ill patients with AKI is quoted to be around 50% and is associated with a six-fold increased risk of dying in the hospital.[2,3] A multinational cross-sectional study on the epidemiology of AKI in ICU patients meeting KDIGO criteria revealed an incidence of 57% with little variation in AKI occurrence and mortality between different parts of the world.[2] Sepsis is among the most common causes of admission to the ICU and is frequently associated with AKI. The pathophysiology of AKI and sepsis is poorly understood,

Table 1. KDIGO and AKIN criteria for diagnosis of AKI

KDIGO	AKIN
Increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours or	Increase in serum creatinine of ≥0.3 mg/dL
Increase in serum creatinine to ≥1.5 times baseline, known to have occurred within the prior seven days	Increase in serum creatinine of ≥50% within 48 hours
Urine volume <0.5 mL/kg/hr for six hours	Urine output of <0.5 mL/kg/hr for >6 hours

Table 2. KDIGO, AKIN and RIFLE staging for AKI. [1,19]

RIFLE	KDIGO	AKIN
Risk: Increase in serum creatinine x 1.5 or decrease in GFR >25% or UOP <0.5 mL/kg/hr for 6-12 hours	**Stage 1**: Increase in serum creatinine of ≥0.3 mg/dL or 1.5-1.9 x baseline or UOP of <0.5 mL/kg/hr for 6-12 hours	**Stage 1**: Increase in serum creatinine of ≥0.3 mg/dL or increase in serum creatinine x1.5-2.0 or UOP <0.5 mL/kg/hr for 6-12 hours
Injury: Increase in serum creatinine x2 or decrease in GFR >50% or UOP <0.5 mL/kg/hr for 12-24 hours	**Stage 2**: Increase in serum creatinine of 2.0-2.9 x baseline or UOP <0.5 mL/kg/hr for 12-24 hours	**Stage 2**: Increase in serum creatinine >200-300% or UOP <0.5 mL/kg/hr for 12-24 hours
Failure: Increase in serum creatinine x 3 or GFR >75% or increase in serum creatinine by >0.5 mg/dL if baseline creatinine is >4.0 mg/dL or UOP of <0.3 mL/kg/hr for >24 hr or anuria for >12 hours or initiation of RRT	**Stage 3**: Increase in serum creatinine of 3.0 x baseline or increase in serum creatinine to ≥4.0 mg/dL or UOP of <0.3 mL/kg/hr for over 24 hours or anuria for over 12 hours or initiation of RRT	**Stage 3**: Increase in serum creatinine >300% or increase in serum creatinine by >0.5 mg/dL if baseline is ≥4.0 mg/dL or UOP of <0.3 mL/kg/hr for >24 hours or anuria for >12 hours or initiation of RRT
Loss: Need for RRT for >4 weeks		
End Stage: Need for RRT >3 months		

UOP: urine output.

Table 3. Summary of the sentinel trials regarding timing of initiation of RRT in critically ill patients with AKI.

Clinical Study	Patients	Study design	N	Study Endpoints	Statistical Significance
ELAIN	Critically ill patients with AKI (KDIGO Stage 2 and higher), mostly surgical	Single center RCT. Early RRT (within 8 hours of KDIGO 2) versus delayed RRT (within 12 hours of KDIGO stage 3 or no initiation)	231	Mortality at 90 days after randomization	Early RRT compared with delayed reduced 90-day mortality
AKIKI	Critically ill medical patients with AKI (KDIGO stage 3)	Multicenter RCT. Early RRT started immediately after randomization, delayed started if patients developed urgent indications or oliguria >72h	620	Overall survival at day 60	Mortality did not differ significantly between early and delayed strategies
IDEAL-ICU	Critically ill patients with early-stage septic shock and AKI (RIFLE)	Multicenter RCT. Early RRT within 12 hours after documentation of failure-stage AKI or delayed at 48 hours if renal recovery had not occurred	488	Death at 90 days	No significant difference in overall mortality at 90 days

though animal models suggest that initially, septic AKI may be caused by a combination of microvascular shunting and tubular cell stress.[4] With resolution of sepsis, the majority of patients with AKI in the context of sepsis have renal recovery though remain at increased risk for developing chronic kidney disease.[4]

The decision regarding whether to start RRT, optimal timing for initiation, modality used, and frequency of RRT in acutely ill patients is an area of ongoing investigation and remains controversial. Many patients will have spontaneous renal recovery and premature initiation of RRT may expose patients to risks such as complications of anticoagulation, hypotension, allergic reactions to system components, and complications of vascular access without conferring meaningful benefit.[5]

TIMING

It is universally accepted that urgent indications for RRT in patients with AKI include severe refractory metabolic acidosis, signs of uremia such as pericarditis or severe encephalopathy, severe refractory hyperkalemia, refractory volume overload, and certain intoxications. In the absence of these clinical scenarios, the optimal timing for initiating RRT among ICU patients remains unclear as there are poor prognostic tools to determine which patients will go on to renal recovery. Some postulate that early removal of uremic toxins and avoidance of hypervolemia may be beneficial in patients who are critically ill, while others contest the risks of vascular access, hemodynamic effects and anticoagulation outweigh the benefits of early initiation. Three large randomized clinical trials comprise the majority of evidence in this arena (**Table 3**).

The ELAIN trial, published in 2016, was a randomized single center parallel group trial, which randomized 231 ICU patients with AKI to early RRT within eight hours of confirmation of KDIGO stage 2 AKI or delayed RRT which was defined as initiation of RRT within twelve hours of either KDIGO stage 3 criteria (**Table 2**) or absolute indications. All patients who received RRT received continuous venovenous hemofiltration (CVVH). The primary outcome of 90-day all-cause mortality was 39.3% in the early group when compared with 54.7% in the delayed group. They also found increased renal recovery at 90 days, a small decrease in median duration of RRT, decreased mechanical ventilation and decreased length of hospital stay in the early group. While striking, this study was limited in that it was single center, almost all patients were surgical patients, and groups were un-blinded. [6]

Within the same year, the AKIKI trial was published. In a large multicenter, open-label randomized trial, 620 ICU patients either mechanically ventilated, or on catecholamine infusions or both, were randomized to receive either early or delayed RRT. When compared with the ELAIN trial, patients were randomized once they developed KDIGO stage 3 AKI (**Table 2**). The early group was randomized and treated within 6 hours of confirming KDIGO stage 3 AKI and the delayed group was treated once acute indications were met based upon laboratory abnormalities or if oliguria or anuria lasted over 72 hours after randomization. There was no significant difference in all-cause mortality at 60 days. Of note, there was a higher incidence of catheter-related blood stream infections in the early RRT group. When compared with the ELAIN trial, these patients were mostly medical ICU patients and over 50% of patients received intermittent hemodialysis and only 30% of patients received CVVH. Also of note, half of the delayed-group patients never received RRT. Post-hoc analysis found the lowest mortality rate among patients who never underwent RRT as compared with those who underwent RRT. [7]

More recently, the IDEAL-ICU trial was published, supporting the results of AKIKI. This was a multicenter randomized trial in which 488 ICU patients with septic shock and AKI were randomized to early initiation of RRT (within 12 hours of onset of RIFLE end-stage kidney disease) (**Table 2**) or delayed initiation (after 48 hours if renal function did not spontaneously recover and if no condition meeting criteria for emergent RRT developed). The primary outcome was

90-day mortality and there was no statistically significant difference between the two groups. There was no significant difference in ICU days between the two groups though fewer patients in the delayed group received RRT and had more RRT free days. The trial was stopped early for futility. Again, post-hoc analysis showed the lowest mortality in patients who never received RRT.[8]

These three major trials all have important differences including number of patients and centers, differences in triggers for early or delayed RRT, and RRT modality. To add to the growing body of literature on the subject, there is an ongoing large phase three trial called STARRT-AKI, in which Rhode Island Hospital is a participating site. STARRT-AKI is including critically ill ICU patients randomized to standard RRT initiation versus accelerated RRT initiation and is due to be published at the end of 2019. A recent meta-analysis of ten randomized controlled trials suggested no additional benefit of early initiation of RRT for critically patients with AKI on 30- 60- or 90-day mortality, though studies included in the meta-analysis had a significant amount of heterogeneity with variable definitions of early versus late RRT.[9] Overall, optimal timing remains unclear but seems to favor delayed RRT with close observation to avoid urgent or emergent indications.

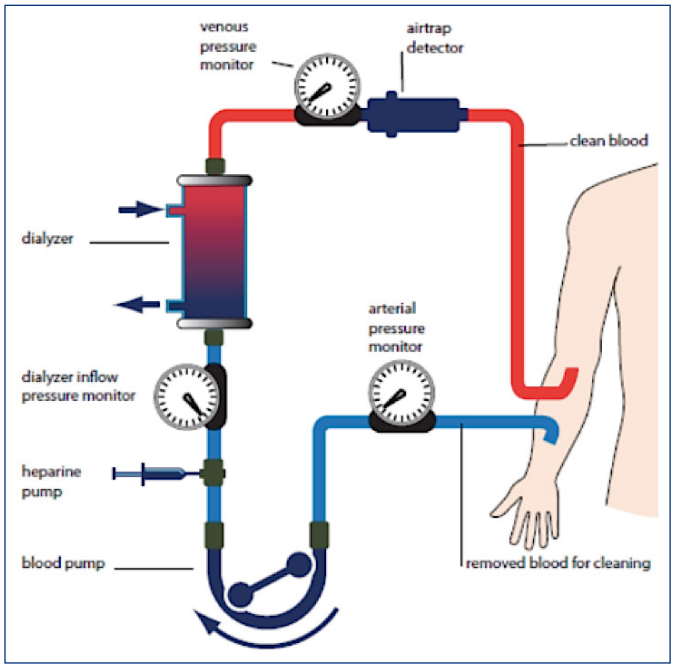
ACCESS

Initial vascular access for patients newly on RRT is usually temporary as the average duration of RRT dependence for patients with AKI is less than two weeks.[5] Historically, femoral access was thought to be associated with an increased risk of catheter-associated line infection; however, more recently a systematic review comparing the rate of catheter-associated line infections in patients with femoral, internal jugular and subclavian lines suggested that there is no significant difference between the three.[10] One exception to this may be among obese patients with a BMI >28.4 where femoral lines have been associated with increased risk of infection.[11] Placement of multiple catheters, longer duration, subclavian access and left internal jugular access are all associated with increased risk of development of central vein stenosis which can compromise the future of arterio-venous fistula and graft placement in the ipsilateral extremity if needed.[12] Tunneled cuffed catheters should be placed in patients who will require long-term RRT (until an arterio-venous fistula or graft can be used) due to the decreased rate of catheter-associated infection.

MODALITY

There are several different types of RRT available for use including intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), peritoneal dialysis (PD), and hybrid therapies including sustained low-efficiency hemodialysis (SLED) (a combined modality where dialysis is administered for hours longer than traditional IHD with slower blood flows but still delivered on a daily basis as opposed to continuously) (**Figure 1**).

Figure 1. Schematic of a hemodialysis circuit.



From Bode, A.S. & Tordoir, Jan. (2013). Vascular Access For Hemodialysis Therapy. Studies in Computational Intelligence. 404. 235-303. 10.1007/978-3-642-27458-9-5)20.

In a prospective randomized multicenter study including critically ill patients with acute renal failure, 60-day mortality was not different between patients who received IHD when compared with CRRT.[13] Additionally, CRRT is associated with higher costs when compared with IHD.[14] A recent systematic review and meta-analysis of 21 studies comparing mortality, dialysis dependence and length of stay among critically ill patients receiving CRRT, IHD or SLED for AKI did not reveal an advantage for any specific RRT modality.[14] KDIGO practice guidelines for AKI recommend using intermittent and continuous RRT modalities as complementary therapies as studies have shown similar survival and recovery of renal function with use of both modalities.[1]

There may be certain circumstances for which a particular modality of RRT may be most beneficial. IHD may be preferential when used for clearance of certain toxicities as poison clearance with CRRT is 50-80% less than that achieved with intermittent modalities.[15] CRRT, on the other hand, is recommended in patients with acute brain injury in whom changes in plasma solute concentration may worsen intracranial hypertension and in concert with systemic hypotension can lead to cerebral hypoperfusion.[16] Additionally, in patients with acute hepatic failure with associated hyperammonemia and high grade encephalopathy, one multicenter cohort study suggested an associated with decreased

ammonia levels and improved 21-day transplant free survival in patients who underwent CRRT as compared with no RRT and IHD.[17] In our center, we have found that when fluid removal is the main purpose of RRT, CRRT allows for increased ultrafiltration as compared with IHD. While used more frequently in the pediatric patient population, there is a paucity of well-designed adult studies comparing the use of PD compared with other RRT modalities in AKI. One prospective, randomized, controlled trial comparing high volume PD with IHD in patients with AKI due to acute tubular necrosis found that mortality rate and renal function recovery were similar in both groups.[18]

CONCLUSIONS

Acute kidney injury in acutely ill adults is associated with high morbidity and mortality and RRT remains an important part of management. Optimal criteria for and timing of initiation remain controversial though the current body of evidence favor delayed initiation with close observation to avoid urgent or emergent indications and minimize the risks of catheter related infection and intradialytic hypotension. Practice guidelines recommend using intermittent and continuous RRT modalities as complementary therapies as studies have shown similar survival and recovery of renal function in the general ICU population.

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