Renal Replacement Therapy in Critically Ill: Current Trend and New Direction

Sarwar Iqbal¹, Mohammad Omar Faruq²

Abstract
Critically ill patients often present with renal dysfunction. Acute kidney injury (AKI) is common in intensive care unit (ICU) patients and is often a component of multiple organ dysfunction syndrome (MODS). Renal replacement therapy (RRT) plays a significant role in management of acute and chronic renal failure in ICU.

During the last decade RRT has made remarkable progress in management of renal dysfunction of critically ill. The Acute Dialysis Quality Initiative conceived in 2002 proposed RIFLE classification for AKI (risk, injury, failure, loss, end-stage kidney disease) using serum creatinine and urine output in critically ill patients. More recently, the Acute Kidney Injury Network (AKIN) has been introduced for staging AKI.

Studies have shown that mortality increases proportionately with increasing severity of AKI. In patients with severe AKI requiring RRT mortality is approximately 50% to 70% according to one study and even a small changes in serum creatinine are associated with increased mortality.

The most common causes of AKI in ICU are sepsis, hypovolemia, low cardiac output and drugs. The various techniques of RRT used in ICU include intermittent hemodialysis (IHD), continuous RRT (CRRT), sustained low efficiency dialysis (SLED) and peritoneal dialysis (PD). It is preferable to use RRT at either RIFLE injury type or at AKIN stage II in critically ill patients.

IHD is commonly used in hemodynamically stable ICU patients. Because of high dialysate (500ml/min) IHD may cause hypotension in some patients. Solute removal may be episodic and often result in inferior uraemic control and acid base control.

CRRT is usually initiated with a blood flow of 100 to 200 ml/min. and thus hemodynamic instability associated with IHD is avoided. Major advantages of CRRT include continuous control of fluid status, hemodynamic stability and control of acid base status. It is expensive and there is high risk of bleeding because of use of high dose of IV heparin.

SLED has been found to be safe and effective in critically ill patients with hemodynamic instability. It uses the same dialysis machine of IHD and combines the effectiveness of CRRT in unstable patients and easy operability of IHD. It is also cost effective.

PD is initiated in ICU for AKI patients when bedside IHD is not available. It is good for hemodynamically unstable patients when IHD or CRRT is difficult. In patients on mechanical ventilator, PD interferes with function of diaphragm causing decrease in lung compliance.

Early identification of AKI with bio markers is an important step in improving outcomes of AKI. These bio markers help early detection of AKI before the onset of rise in serum creatinine. Serum cystatin C is one of the sensitive bio markers of small changes in Glomerular filtration rate (GFR) and has been found to be useful.

AKI in the ICU most commonly results from multiple insults. Therefore appropriate and early identification of patients at risk of AKI provides an opportunity to prevent subsequent renal insults. This strategy will influence overall ICU morbidity and mortality.

Key words: AKI in ICU, RRT, SLED, PD, CRRT

Introduction
Acute kidney injury is common in critically ill patients and is associated with significant morbidity and mortality. Diagnosing and managing critically ill patients with renal dysfunction is an important part in the management of critically ill. Renal replacement therapy (RRT) is being widely used in intensive care. Acute kidney injury (AKI) is frequently present in critically ill patients of the intensive care unit (ICU) as a part of multiple organ dysfunction syndrome (MODS). These patients have various co-morbid conditions and are on various life-supportive modalities. Fluid overload and electrolyte and acid-base disturbances and drugs may further injure their organ systems. RRT plays a significant role in ICU in the treatment of patients with renal failure, acute as well as chronic. However, the term ‘RRT’ is not

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accurate as it is not possible for dialysis to replace all
functions of the kidney. ‘Renal support therapy’ would be a
better terminology to refer to this modality of treatment1. The
field of RRT has undergone remarkable changes over the last
decade and has been evolving rapidly.

Acute kidney injury (AKI), previously termed acute renal
failure, refers to a sudden decline in kidney function causing
disturbances in fluid, electrolyte, and acid–base balance
because of a loss in small solute clearance and decreased
glomerular filtration rate (GFR). The nomenclature shift to
AKI describes more perfectly the spectrum of disease from
subclinical injury to complete organ failure.

**Defining AKI in ICU**

More than 35 definitions of AKI currently exist in the
literature2. The Acute Dialysis Quality Initiative convened in
2002 and proposed the RIFLE classification (risk, injury,
failure, loss, end-stage kidney disease) specifically for AKI
using serum creatinine and urine output in critically ill
patients. More recently the Acute Kidney Injury Network
(AKIN) has been introduced for staging AKI.

The RIFLE classification3 was proposed by the Acute
Dialysis Quality Initiative specifically for AKI in critically ill
patients. The Acute Kidney Injury Network (AKIN) criteria4
further modified the RIFLE criteria (Table I). The most
current consensus diagnostic criteria for AKI is “an abrupt
(within 48 hours) reduction in kidney function, currently
defined as an absolute increase in serum creatinine of ≥0.3
mg/dL (≥26.4 μmol/L), a percentage increase in serum
creatinine of ≥50% (1.5-fold from baseline), or a reduction in
urine output (documented oliguria of <0.5 ml/kg/hr for > 6
hours).”

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<th>RIFLE</th>
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<td>Increase in S.Cr ≥1.5 baseline or decrease in GFR ≥25%</td>
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<td>Increase in S.Cr ≥26.2 mmol/L or increase to ≥150-199% (1.5 to 1.9 fold) from baseline</td>
<td>&lt;0.5ml/kg/hr ≥6 hrs</td>
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<td>Increase in S.Cr ≥2.0 baseline or decrease in GFR ≥50%</td>
<td>&lt;0.5ml/kg/hr ≥12 hrs</td>
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<td>Increase in S.Cr ≥200-299% (&gt;2-2.9 fold) from baseline</td>
<td>&lt;0.5ml/kg/hr ≥12 hrs</td>
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<td>Increase in S.Cr ≥3.0 baseline or decrease in GFR ≥75% or absolute S.Cr ≥354 mmol/L with an acute rise of at least 44 mmol/L</td>
<td>&lt;0.3ml/kg/hr ≥24 hrs or anuria ≥12 hrs</td>
<td>3</td>
<td>Increase in S.Cr ≥300% (≥3 fold) from baseline or S.Cr ≥354 mmol/L with an acute rise of at least 44 mmol/L or initiation of RRT</td>
<td>&lt;0.3ml/kg/hr ≥24 hrs or anuria ≥12 hrs</td>
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*AKIN = Acute kidney injury network, GFR = Glomerular filtration rate, RIFLE = Risk, injury, failure, loss, end-stage kidney
disease, S.Cr = Serum creatinine, UOP = Urine output

**Epidemiology of AKI in ICU**

AKI in the ICU is common, increasing in incidence5,6 and is
associated with a substantial increase in morbidity and mortality7,8. AKI occurs in approximately 7% of all hospitalized patients9 and in up to 36% to 67% of critically ill patients depending on the definition used10. Based on 75,000 critically ill adults, more severe AKI occurs in 4% to 25% of all ICU admissions8,10. On average, 5% to 6% of ICU patients with AKI require renal replacement therapy (RRT). Reported mortality in ICU patients with AKI varies considerably between studies depending on AKI definition and the patient population studied (e.g., sepsis, trauma, cardiothoracic surgery, or contrast nephropathy). In the majority of studies, mortality increases proportionately with increasing severity of AKI11. In patients with severe AKI requiring RRT, mortality is approximately 50% to 70%12. While AKI
requiring RRT in the ICU is a well-recognized independent
risk factor for in-hospital mortality13, even small changes in
serum creatinine (S. Cr) are associated with increased
mortality. Notably, multiple studies of patients with AKI and
sepsis, mechanical ventilation, major trauma, cardiopulmonary bypass, and burn injuries have consistently
demonstrated an increased risk of death despite adjustment for co morbidities and severity of illness. Morbidity, a less
appreciated consequence of AKI in the ICU, is associated
with increased cost, increased length of stay, and increased
risk of chronic kidney disease (CKD), including end-stage
kidney disease14. The true incidence of CKD after AKI is
unknown because epidemiologic studies do not routinely or
consistently report rates of renal recovery and those that do
use variable definitions.

**Common causes of AKI in ICU**

The most common causes of AKI in the ICU are sepsis,
hypovolemia causing renal hypoperfusion, low cardiac output
and drugs. Other common causes include hepatorenal
syndrome, rhabdomyolysis, urinary flow obstruction, trauma,
surgery etc. Angiotensin Converting Enzyme (ACE) Inhibitor and Angiotensin II Receptor Blocker (ARB) are other potential aggravating factors in the development of AKI and thus, renal function should be checked at three to five days interval when an ACE inhibitor or ARB is prescribed in a patient who is at risk for AKI.

**Indications of RRT**
Severe AKI results in deregulation in the homeostasis of fluid, potassium, metabolic acids, and waste products. RRT aids to prevent life-threatening complications and to improve homeostasis.

Prevailing criteria for the initiation of RRT in ICU include

- Oliguria (urine output <200 ml/12 h)
- Anuria (urine output: 0–50 ml/12 h)
- Blood urea > 35 mmol/L (>98 mg/dL)
- Serum creatinine > 400 mmol/L (>4.5 mg/dL)
- Uncompensated metabolic acidosis (pH < 7.1)
- Serum K+ > 6.5 mmol/L or rapidly rising values
- Serum Na+ >160 mmol/L
- Pulmonary edema refractory to diuretics
- Uremic complications (encephalopathy/pericarditis)
- Overdose with a dialyzable toxin
- Hyperthermia and hypothermia

Additional indications for RRT are

- Cardiac failure
- Patients requiring a large amount of fluid, parenteral nutrition or blood products, but at risk of developing pulmonary edema or ARDS
- Hyperthermia (core temperature >39.5°C) or hypothermia (core temperature <37°C)

AKI in the ICU often occurs as a part of MODS, and such patients may have less tolerance of metabolic derangements, such as acidosis and electrolyte imbalances. RRT should be initiated in these patients before the development of extreme metabolic derangements. In patients who require renal support because of metabolic derangements, RRT should not be delayed.

It is preferable to commence RRT at either RIFLE injury stage or at AKIN stage II in critically ill patients when both criteria (urine output and serum creatinine) are included.

**Modes of RRT:** The common modes include,

- **Intermittent Hemodialysis (IHD)**
- **Continuous RRT (CRRT)**
- **Sustained Low Efficiency Dialysis (SLED)**
- **Peritoneal Dialysis (PD)** which can be done by either of the following.
  a) **Continuous Ambulatory Peritoneal Dialysis (CAPD)** by a rigid catheter.
  b) **Continuous Ambulatory Peritoneal Dialysis (CAPD)** conventional or cycler assisted by a flexible (Tenckhoff) catheter.

**Intermittent Hemodialysis (IHD)**
This technique uses high dialysate flows (500 ml/min). Treatment is applied for short periods of time (3 – 4 hours), usually every other day.

IHD has several disadvantages. A reasonably large volume of fluid has to be removed over a short period of time, which can result in hypotension. Repeated hypotensive episodes may delay renal recovery. The use of CRRT is preferred for its improved cardiovascular tolerance over daily intermittent hemodialysis. Solute removal in IHD is episodic. This results in inferior uremic control and acid-base control. Limited fluid and uremic control imposes unnecessary limitations on nutritional support. Rapid solute shifts may increase brain water content and increase in intracranial pressure. Standard low-flux dialyzing membranes trigger the activation of several inflammatory pathways when compared to high-flux synthetic membranes (also used for continuous haemofiltration). This pro-inflammatory effect contributes to further renal damage and delays recovery or even affects mortality.

**Continuous RRT (CRRT)**
The hemodynamic instability that is often associated with IHD, along with the risk of injury to the recovering kidney, led to the invention of Continuous renal replacement therapy (CRRT) techniques. CRRT is usually initiated with a blood flow of 100 mL/min and gradually increased up to 200 mL/min. CRRT is inherently complex with the requirement for anti-coagulation and the use of high volumes of fluid and is much costlier compared to IHD.

The advantages of CRRT include continuous control of fluid status, hemodynamic stability, control of acid–base status, ability to provide protein-rich nutrition while achieving uremic control, control of electrolyte balance including phosphate and calcium balance, prevention of swings in intracerebral water, minimal risk of infection, and high level of biocompatibility. CRRT has to be considered for patients with cerebral edema, severe hemodynamic instability, persistent on-going metabolic acidosis, and large fluid removal requirements.

Disadvantages of CRRT include higher risk of bleeding due to higher dosage of heparin required, restricted patient mobility. It requires trained personnel and it is expensive.

**Sustained Low Efficiency Dialysis (SLED)**
Hybrid therapies like SLED and extended daily dialysis have been shown to be safe and effective in critically ill patients. Slow low efficiency diatilfiltration (SLED-f) by combining SLED with ultrafiltration has been shown to provide stable renal replacement therapy.

SLED has better hemodynamic tolerability. It involves no extra machine or device. It combines the effectiveness of CRRT in hemodynamically unstable patients and easy operability of IHD. It involves less heparin dosages and is cost effective. SLED is better for hemodynamically unstable cardiac patients.
Peritoneal Dialysis (PD)

Peritoneal dialysis (PD) was the first modality of renal replacement therapy used for AKI patients. In the 1970s, acute PD was widely accepted for AKI treatment, but its practice declined in favor of hemodialysis in the 1980s. It is frequently used in developing countries because of its lower cost and minimal infrastructural requirements. Recently, interest in using PD to manage AKI patients has been increasing. One important question is whether PD can provide adequate metabolic and fluid control for treating AKI patients.

The work by Gabriel et al. showed that, with careful thought and planning, PD could successfully treat critically ill patients. To overcome some of the classic limitations of PD use in AKI, such as a high chance of infection and no metabolic control, they proposed the use of cycles, flexible catheter, and a high volume of dialysis fluid.

In peritoneal dialysis, 1.5 – 3 L of peritoneal dialysate solution is infused into the peritoneal cavity and allowed to dwell for a set period of time, usually 2 to 4 hours. A combination of convective clearance and diffusive clearance occurs. The clearance of solutes and water depends on the balance between the movement of solutes and water into the peritoneal cavity versus absorption from the peritoneal cavity into the peritoneal capillary circulation across the peritoneal membrane. The rate of diffusion diminishes with time and eventually stops when equilibration between plasma and dialysate is reached. PD in ICU is indicated when the patient is so hemodynamically unstable that transport to the dialysis unit situated away from the ICU is forbidden. This is especially true when bedside haemodialysis is not available in ICU. PD is found to be more effective in AKI in extremes of age i.e. pediatric patients and elderly patients.

PD is good for hemodynamically unstable patients where IHD or CRRT is difficult. There are no hazards of heparin. Insulin may also be added in patients with diabetes mellitus. A non-absorbable carbohydrate osmotic agent, icodextrin, has been found to be associated with more efficient ultrafiltration than dextrose-containing solutions. PD is also a cheap modality of treatment for AKI in resource poor countries.

Disadvantages of PD include peritonitis, weight gain, hyperglycemia, fluid leaks, protein loss and interference with diaphragm function reducing lung compliance especially when patient is receiving positive pressure breathing by mechanical ventilator.

Current trend in RRT

Results from a large prospective multi-centered observational study of 1200 patients were inconsistent and dependent on the definition of “early” or “late” initiation of RRT. In this study, “late” initiation of RRT was associated with worse outcomes (higher crude mortality, longer duration of RRT, increased hospital length of stay, and greater dialysis dependence) when “late” was defined relative to date of ICU admission. A recent meta-analysis nine randomized trials (RCT) comparing intermittent to continuous renal replacement therapy (intermittent RRT vs. CRRT) in AKI demonstrated no difference in mortality or renal recovery defined as independence from RRT. Two studies have shown that CRRT is associated with better long-term kidney recovery when compared to intermittent RRT. In contrast, four RCT that included renal recovery as a primary outcome showed no difference in need for chronic RRT. In the absence of definitive data in support of a particular modality, the choice of RRT modality is currently influenced by multiple factors, including individual site availability, expertise, resources, cost, and likely clinician bias. Hybrid therapies include SLED and extended daily dialysis. These modalities utilize standard intermittent hemodialysis machines but provide a slower solute and fluid removal similar to CRRT technologies. Although there have been no prospective randomized trials evaluating outcomes, hybrid therapies have been shown to be safe and effective alternatives to treating AKI in critically ill patients. The question of optimal modality has not yet been definitively answered. According to several studies in critically ill patients, serum cystatin C is better than S.Cr for early detection of AKI and as a more sensitive marker of small changes in GFR. However, in one smaller study there was no correlation between cystatin C and S.Cr. In a recent study, urinary cystatin C but not plasma cystatin C was a sensitive marker of small changes in GFR. In a recent study, urinary cystatin C but not plasma cystatin C was a sensitive marker of small changes in GFR. In a recent study, urinary cystatin C but not plasma cystatin C was a sensitive marker of small changes in GFR. In a recent study, urinary cystatin C but not plasma cystatin C was a sensitive marker of small changes in GFR. In a recent study, urinary cystatin C but not plasma cystatin C was a sensitive marker of small changes in GFR.

Future trends

Early identification of AKI with novel candidate biomarkers is an important step in improving outcomes in AKI. These biomarkers help not only in early detection of AKI but also in the onset of a rise in the serum creatinine, but also in the differential diagnosis and prognosis. Serum cystatin C is a sensitive marker of small changes in GFR and has been found to be a useful biomarker for early detection of AKI. In a recent study, urinary cystatin C was found to be superior to conventional plasma markers in the early identification of AKI in post-cardiac surgery patients. Most promising early biomarkers of AKI are neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin (IL) -18.

Prevention of AKI in critically ill: A novel approach

Those patients prone to develop AKI as evidenced by early biomarkers and with hypotension can use intra-aortic balloon counter pulsation set just below the renal arteries to ensure perfusion of both the kidneys. This approach is hypothetical and requires study on experimental animals and then on human subjects.

Conclusion

The field of RRT has made remarkable progress over the last decade and is continuing to evolve rapidly. CRRT is now firmly established throughout the world and is perhaps the most commonly used form of RRT. CRRT seems to be superior to IHD with regard to physiological end points. Modifications of IHD, such as SLED, are able to combine the advantages of both IHD and CRRT. PD particularly CAPD is emerging mode of RRT in critically ill. AKI in the ICU most commonly results from multiple insults. Therefore, appropriate and early identification of patients at risk for AKI provides an
opportunity to prevent subsequent renal insults and ultimately influence overall ICU morbidity and mortality. Strategies to prevent AKI in these patients are of crucial importance. Critical care nephrology is a fast-emerging subspecialty, and critical care physicians are likely to play a paramount role in the management of patients with renal failure.

References


