CHAPTER

123

AKI in ICU – Diagnosis and Management

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Acute kidney injury (AKI) is a rapid decrease in kidney function over hours to days, due to an an injury that causes functional or structural changes in the kidneys, resulting in inability to maintain acid-base, fluid and electrolyte balance and to excrete nitrogenous wastes. AKI is a complex disorder that comprises the entire spectrum of acute renal failure for which currently there is no accepted definition. To establish a uniform definition for AKI, the ADQI formulated the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) classification.RIFLE defines three grades of increasing severity of acute kidney injury- risk (class R), injury (class I) and failure (class F)- and two outcome classes (loss and end-stage kidney disease)(see Table 1). Here, the grades of severity of AKI is based on changes in either serum creatinine or urine output from their baseline condition over 7 days. The AKIN criteria formulated more sensitive criteria as given in Table 2 in which a 0.3mg/dl rise in creatinine over 48 hours was considered AKI. KDIGO in 2012 combined these two criteria and came up with the latest classification of AKI (Table 3).

Table 1: Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification

Class	Glomerular filtration rate criteria	Urine output criteria
Risk	Serum creatinine × 1.5	< 0.5 ml/kg/hour × 6 hours
Injury	Serum creatinine × 2	< 0.5 ml/kg/hour × 12 hours
Failure	Serum creatinine × 3, or serum creatinine ≥ 4 mg/dl with an acute rise > 0.5 mg/dl	< 0.3 ml/kg/ hour × 24 hours, or anuria × 12 hours
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks	
End-stage kidney disease	End-stage kidney disease > 3 months	

Table 2: AKIN Classification

AKIN CRITERIA	
Creatinine criteria Creatinine – ≥0.3 mg/dl	**Urine output – Criteria** UO <0.5 mL/ kg/h for 6 h
Risk or Stage 1 Creatinine ≥150% and < 200% than baseline	
Injury for stage 2 Creatinine≥ 200% and <300% than Baseline	UO <0.5 mL/kg/h for 12 h
Failure or stage 3 Creatinine ≥300% than baseline Or ≥4.0 mg/dl and ≥ 0.5 mg/dl	UO <0.3 mL kg/h for 24 h, or anuria for 12 h

ETIOLOGY OF AKI

Acute kidney injury is anatomically classified (Figure 1) into three categories: pre-renal causes (kidney hypoperfusion leading to low GFR), renal causes (intrinsic kidney diseases like glomerulonephritis GN,Acute tubular necrosis ATN, acute interstitial nephritis AIN etc) and post renal causes (obstructive uropathy or other obstruction to outflow). Identifying the cause is the step toward treating the patient.

GLOBAL STATUS AND INDIAN SCENARIO

The incidence rate of acute kidney injury (AKI) around the world is not well known Acute Kidney Injury is common, complicating 5% of all medical and surgical admissions

Table 3: KDIGO Criteria

Stage	Serum creatinine (SCr) criteria	Urine output criteria
1	Increase >26 umol/l within 48 hours OR Increase > 1.5 to 1.9 x reference SCr	<0.5 ml/kg/hour for >6 consecutive hours
2	Increase ≥2 to 2.9 x reference SCr	<0.5ml/kg/hour for >12 hours
3	Increase >3 x reference SCr OR increase >354u.mol/l OR commenced on renal replacement therapy (RRT) irrespective of the stage	<0.3ml/kg/hr for >24 hours or anuria for 12 hours

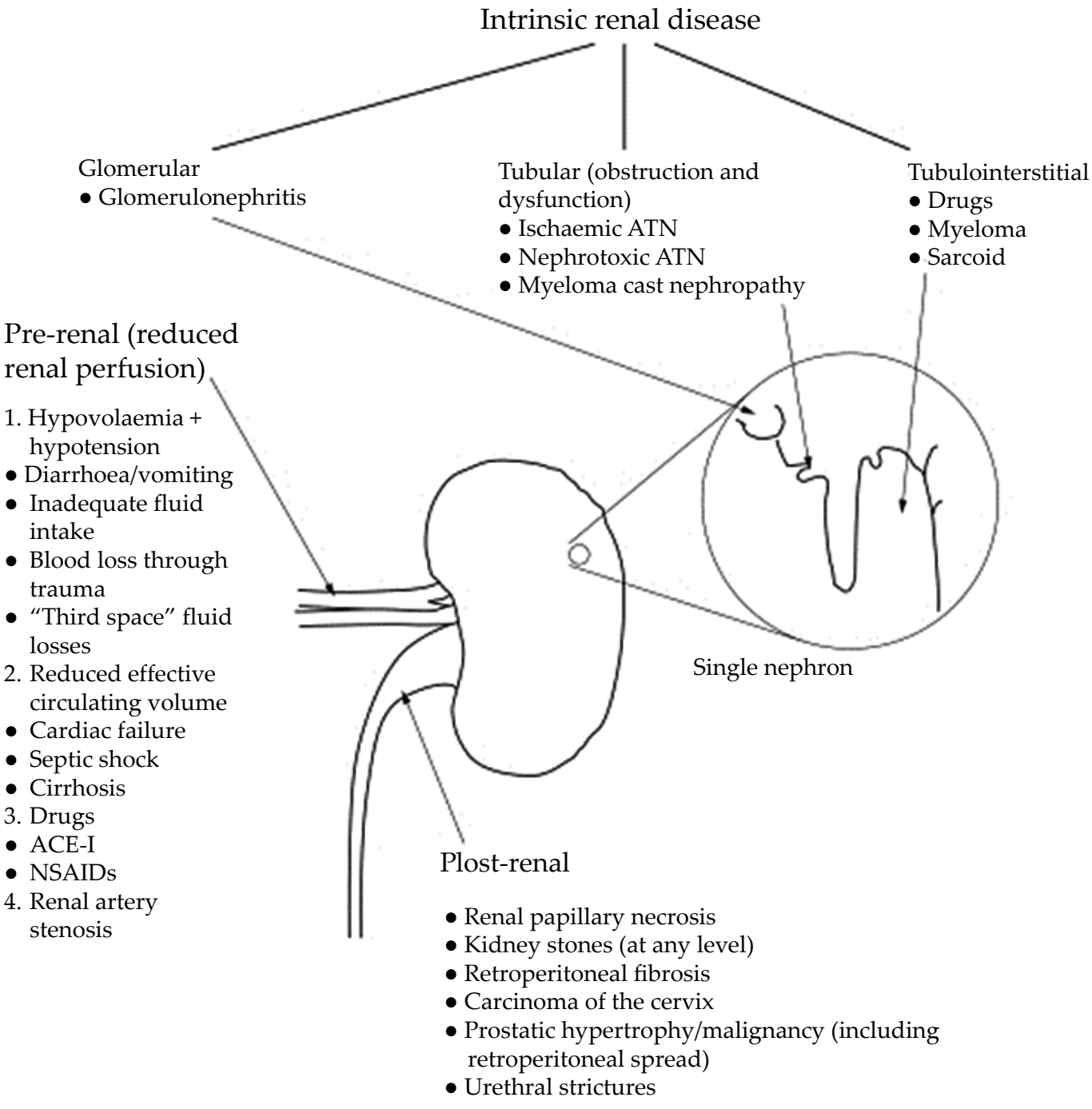

Fig. 1: Anatomical classification of acute kidney injury and its causes

in a large American study. Age wise 17 cases annually per million population aged 16-50 years rising to 949 cases annually per million population in those aged 80-89 years. The relatively wide disparity in reported incidence rates and the increasing frequency of the condition raise concerns as to the real magnitude of the problem.

It is recognized that the epidemiology of AKI in developing countries differs from that of the developed countries in many important ways.Whereas in developed regions elderly patients predominate, in developing countries, AKI is a disease of the young and children but the trend shows an increasing incidence in older population in India as diagnostic tools are available in secondary care private and government hospitals.The case of critically ill patients in ICU involves effective multi disciplinary approach, evidence based practice protocols and clear communications with patients relatives and cost effective modalities of treatment.

Overall mortality seems to be lower in developed countries, However in developing countries while taking age group into consideration, among children and the young, mortality is high. In developing countries, the most common causes of AKI are frequently seen with volume-responsive "prerenal", obstetric, infectious, or toxins thus inexpensive, simple interventions such as education on oral rehydration, improved cross-cultural

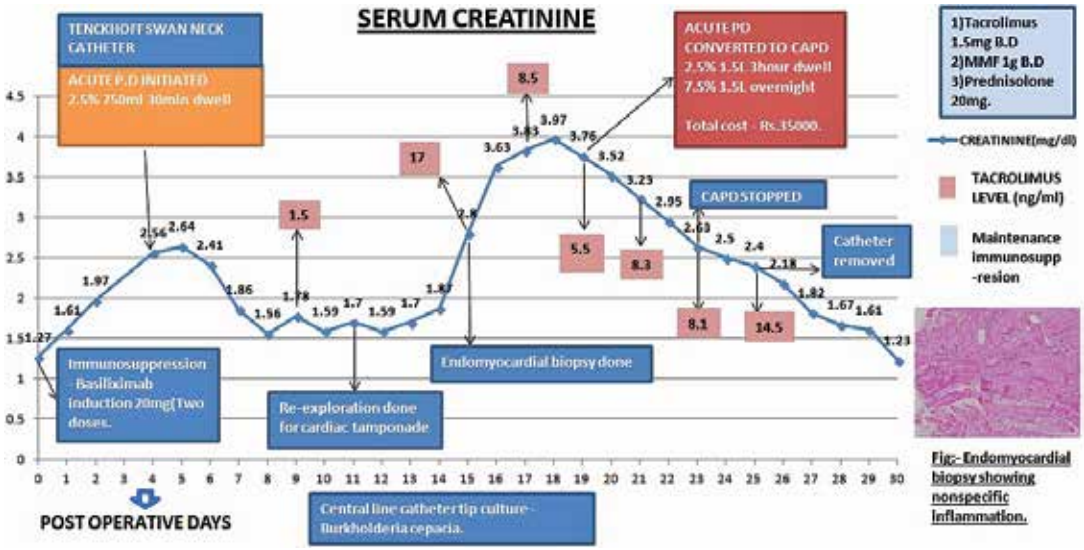

Fig. 2: Clinical course and biochemical parameters and biopsy picture

interaction with traditional healers, change in obstetric management policies, or management of infection may result in a dramatic reduction in the incidence and severity of AKI. Renal causes like acute glomerulonephritis, both primary and secondary to infectious diseases appears to be higher than in developed countries. Malaria represents an especially important problem. There is an upsurge in worldwide malarial incidence. In India, for example, the overall yearly incidence is 13 to 17.8% of malarial cases. Given that in developing countries the costs of renal replacement therapies are prohibitively high, prevention is often the only realistic way to decrease the incidence of AKI.

HOW IS AKI IN ICU DIFFERENT FROM OTHER HOSPITAL SETTINGS?

AKI is very commonly encountered in ICU, medicine and surgical settings. It is common in critically ill patients and occurs in 18-65% of adult patients admitted in ICU. Upto 20% of patients who develop AKI require Renal replacement therapy (RRT) in ICU and carry high mortality,in excess of 50 percent. While the critically ill AKI patients have varible presentation:some have multiple organ failure, sepsis, hypervolemia, acute respiratory distress and underlying co-existing CKD. Patients with ischemic stroke who may have multiple medications and nutritional needs requires special attention. Consequently clinicians must distinguish patients who may recover spontaneously from those who will require renal replacement therapy (RRT). In addition, the benefits of RRT must be weighed against its inherent risks. Similarly, different schools of thoughts still exist regarding the choice of type of dialysis-haemodialysis or peritoneal dialysis in ICU settings. BP targets of 65 to 70 mm Hg vs 80 to 85 mm Hg inpatient with septic shock, a large randomized clinical trial conducted in France (sepsis and mean arterial pressure trial) did not show a benefit to higher blood pressure targets. In patients with chronic hypertension there is a significant interaction between BP and renal outcomes. In patients with chronic hypertension those randomized to the higher BP target had lower rates of doubling of serum creatinine and the need for renal replacement therapy over the first seven study days.

Here we describe AKI in a heart transplant recipient in the immediate post operative period who was critically ill. A female medical doctor 40 years age weighing 75 kg, with hypertrophic non-obstructive cardiomyopathy who was previously implanted with intracardiac defibrillator has undergone cardiac transplantation on july 13, 2016 Cold ischemia time was 249 minutes. She was inducted with with Basiliximab 20mg (two doses) and maintenance immunosuppression included tacrolimus, mycophenolate mofetil and prednisolone.

Postoperatively she developed fever with non-oliguric AKI and sepsis. Inotropes and ventilatory support were continued. X ray chest showed bilateral lower zone infiltrates. Blood cultures and central venous catheter tip culture revealed growth of Burkholderia cepacia. She was treated with tigecycline 50 mg once a day and meropenam 500 mg once daily as per the renal dose. On the third postoperative day she developed acute pulmonary edema and hypotension. Echocardiography confirmed cardiac tamponade. She was re-explored and 500ml fresh blood with clots were evacuated from pericardium. Tenckhoff Swan-neck double-cuff peritoneal dialysis (PD) catheter was implanted. Low volume intensive PD was commenced with 750ml, 30 minutes dwell time and alternating 1.5 %, 2.5% and 4.25 % dianeal dialysis solution to produce adequate ultrafiltration to decongest the lungs. Dedicated peritoneal dialysis nurses manually did exchanges. Fill volume was not increased to prevent pericatheter leakage. Patient continued to have recurrent episodes of pulmonary edema for continuous supine peritoneal dialysis was continued with the low volume and short dwells till the eighteenth postoperative day. Endomyocardial biopsy was done on the fifteenth postoperative day which showed nonspecific inflammation and no evidence of acute rejection. Acute

PD was converted to Continuous ambulatory peritoneal dialysis (CAPD) from nineteenth postoperative day. Tacrolimus levels were monitored and dosages were adjusted accordingly. Patient gradually recovered from sepsis and fluid overload. As patient developed a pericatheter leak on the twenty third postoperative day, peritoneal dialysis was stopped and PD catheter was removed. Echocardiography on discharge showed a left ventricular ejection fraction of 50%. Patients renal function recovered by twenty eighth postoperative day. The sequential renal function, immunosuppressive agents and clinical course are depicted in Figure 2. The total cost of peritoneal dialysis during the hospital stay of 30 days was Rs.35000.

Another issue is that in ICU, AKI is a common accompaniment in multiple organ failure. It is not uncommon for critically ill patients to be on multiple supports including inotropes and ventilators.

Similarly, when the AKI is due to sepsis and multi organ failure, thrombocytopenia, coagulation abnormalities and bleeding from various sites are common, need for anticoagulation during extra corporeal therapies adds to bleeding risk. PD offers a significant advantage of not needing anticoagulation and a bedside single access with a flexible catheter.

Hyperchloremic metabolic acidosis is the leading cause of acidosis in the early stages of AKI. This is due to the decreased regeneration of bicarbonate by the kidneys with an inability to excrete ammonium ions. Later, the accumulation of anions, such as phosphate, sulphate,urate ,hippurate,propionate, and oxalate, may lead to high anion gap acidosis. Lactic acidosis is also common in critically ill patients with AKI in shock. There is uncertaintly about the need to correct mild to moderate metabolic acidosis in the setting of AKI, further more, studies do not support the routine use of sodium bicarbonate infusion to treat lactic acidosis. However most experts believe that the use of bicarbonate is appropriate in patients with severe lactic acidosis and appropriate in patients with severe lactic acidosis and academia (arterial PH <7.1). Such severe academia may produce hemodynamic instability as a result of reduced left ventricular contractibility, arterial vasodilation, and impaired responsiveness to catecholamines.

What is sepsis

Sepsis : Life threatening organ dysfunction due to dysregulated host response infection.

Clinical criteria. An increase in the sequential (sepsis-related) organ failure assessment (SOFA) score of 2 points or more due to infection itself.

Rationale : This increase in SOFA score is associated with in hospital mortality > 10%

Septic shock : A subset of sepsis in which circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone.

Clinical criteria : Need for vasopressor therapy to maintain mean arterial pressure > 65 mm Hg and serum lactate > 2 mmol/L after volume resuscitation.

Rationale : patients who meet these clinical criteria have inhospital mortality rates >40%.

Intra – abdominal hypertention

Intra abdominal pressure (IAP) is the steady state pressure concealed within the abdominal cavity Normal value ranges from 0 to 5 mm Hg in healthy adults. Intra-abdominal hypertension (IAH) and abdominal compartments syndrome are increasingly recognized in both medical and surgical critically ill patients are predictive of death and the development of AKI. Although there are many risk factors for the development of IAH, in the era of goal–directed therapy for shock, brisk volume resuscitation and volume overlad are the most common contributors.Lowering intra-abodiminal pressure and increasing abdominal perfusion pressure may ameliorate or prevent AKI. Liberal use of vasopressors and volume removal can improve AKI and the resolve distend end organ effects of IAH.

MANAGEMENT

AKI in ICU the leading cause is sepsis. The initial clinical approach is identical in all patients- a thorough history and examination with simultaneous treatment of any life threatening features (severe hyperkalaemia > 7.5 mmol/L). Subsequent management should focus on determining the cause, which may demand specific treatment, maintaining the patient's volume status, and avoiding further nephrotoxic insults (Figure 3).

Clinical approach to patients

The twin foundations of the approach to the patient with AKI are to:

1. Treat any life threatening features: Hypotension, shock and respiratory failure should be immediately apparent when assessing the patient, and clearly these demand urgent treatment. Hyperkalaemia is less likely to be immediately obvious. Unless changes are evident on ECG or cardiac monitoring, it will only become apparent when chemistry is available.
2. Identify any cause of AKI that warrants specific treatment: Many patients with AKI present with other diagnoses. Dehydration secondary to gastrointestinal losses, pneumonia, bowel obstruction, and new impairment of functional capacity in the elderly patient are often the initial "on take" diagnose and a diagnosis of kidney injury is only made when laboratory parameters are available later. The clinician should then ask themselves the following questions:

Diagnosis of AKI in ICU

Critical care ultrasound can meaningfully expedite and improve the diagnosis of the underlying cause of organ dysfunction in the critically ill. Critical care ultrasound is not a replacement for formal imaging studies. Critical care ultrasound applications that may be of particular

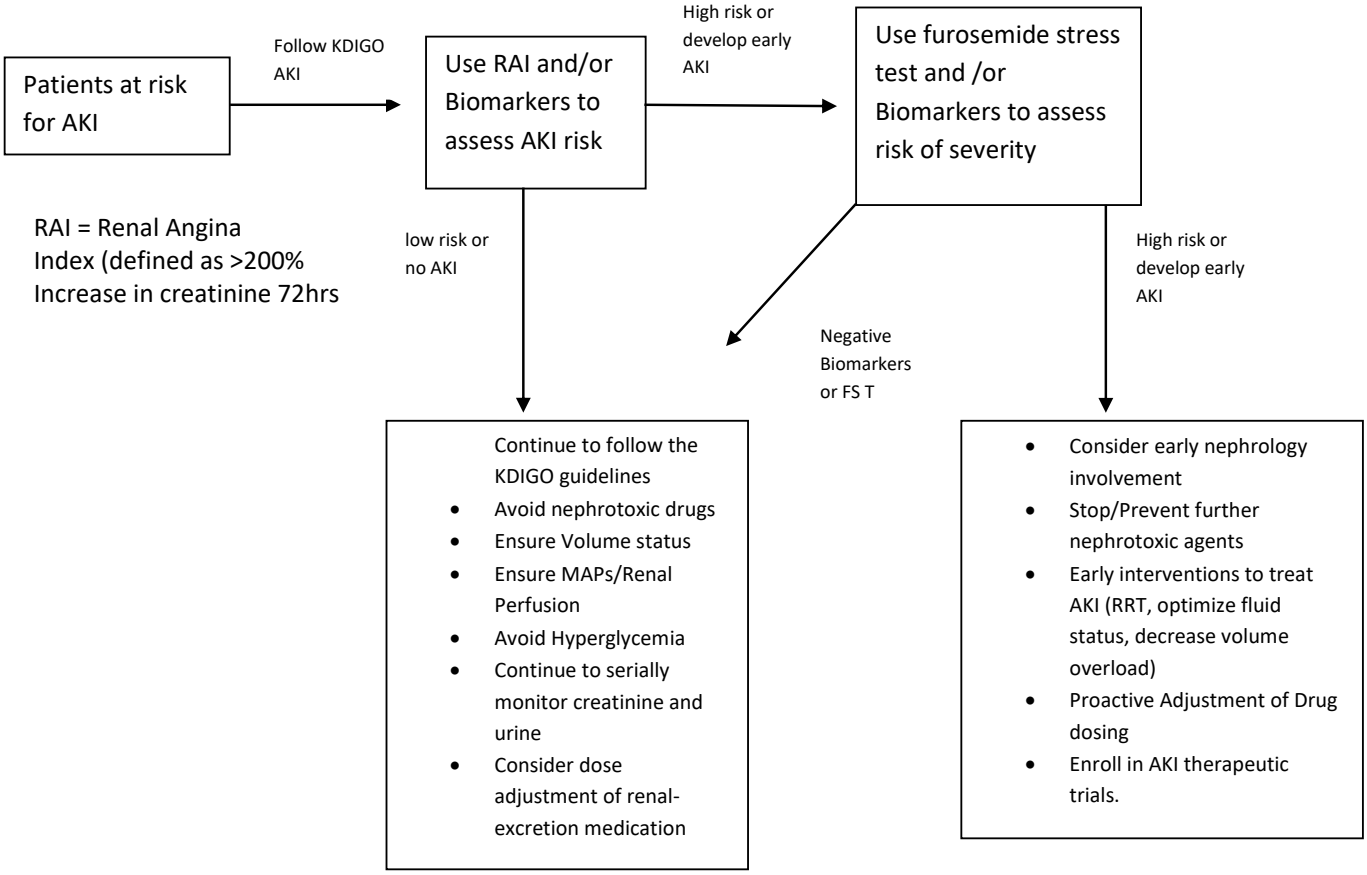

Fig. 3: Potential work flow for use in high risk for AKI

relevance to the nephrologist include renal ultrasound in patients at high risk for urinary tract obstruction, real time ultrasound guidance and verification during the placement of central venous catheters, and ultrasound-augmented assessment of shock volume status.

Improved AKI risk stratification techniques need to be developed as they may be used to better inform timing decisions for RRT initiation and AKI therapeutics.

Several AKI risk prediction scores and kidney specific scoring models have been developed and validated in the setting of cardiac surgery: however most of these scores fail to predict milder form of AKI. Many novel AKI risk assessment techniques have been developed over the past 5 – 10 years including Renal Angina Index, functional and damage biomarkers, and the furosemide stress test: however these methods still require large scale validation. Urinary levels of tissue inhibitor of metalloproteinase 2 (TIMP-2) and Insulin like growth factor binding protein 7 (IGFBP 7) is approved to detect a early severe AKI in the new era of biomarker utilization. IL- 18, KIM – 1 cystatin C are other biomarkers for early detection of contrast induced AKI. Currently available risk scores to predict AKI are often not sensitive or specific enough to identify high risk individuals and poorly predict AKI progression. With early administration of appropriate antibiotics, volume resuscitation, and source control, mortality has declined from sepsis. Early goal- directed therapy with central venous pressures monitoring is not needed in all patients.

Dynamic ultrasound measurement of inferior vena cava (IVC) half shown to predict volume responsiveness in shock. IVC respiratory variation in mechanically ventilated patients with septic shock (SBP < 90 mm Hg or use of vasopressors showed absolute IVC distensibility was found to be predictive of volume responsiveness to shock (distensibility of 12%). IVC collapsibility of > 40% should prompt the clinician to administer a fluid challenge, but collapsibility of < 40% is not helpful.

Low tidal volume ventilation is lifesaving for patients with the acute respiratory distress syndrome : additional studies are needed to confirm the potential benefit of prone positioning and neuromuscular blockade in patients with moderate to severe acute respiratory distress syndrome. Proton pump inhibitors should be used judiciously for gastrointestinal prophylaxis, given an increased risk of acute kidney injury and incident CKD, along with an increased risk of Clostridium difficile infection.

Serum creatinine and urinary output have inherent limitations in the early diagnosis of AKI.

In patients who are critically ill in ICU, the measured serum creatinine may under estimate the GFR and hence a correction should be done to over come the limitation. Correction factor for Creatinine in volume overload. Adjusted serum creatinine = Serum creatinine ×correction factor,where correction factor = [hospital admission weight (kg) ×0.6] + Σ(daily cummulative fluid balance (L))] Hospital admission weight ×0.6.

Table 4: Advantages and disadvantages of intermittent versus continuous renal replacement therapy

	Intermittent haemodialysis	Continuous therapy
Advantages	Lower risk of systemic bleeding	Better haemodynamic stability
	More time available for diagnostic and therapeutic interventions	Better fluid control Better biochemical control
	More suitable for severe hyperkalaemia	Better pulmonary gas exchange
	Lower cost	Improved nutritional support
	Fewer cardiac arrhythmias	
	Shorter stay in ICU	
Disadvantages	More difficult haemodynamic control	Higher risk of systemic bleeding
	Availability of dialysis staff	Greater vascular access problems
	Inadequate dialysis dose	More filter problems
	Inadequate fluid control	More immobilisation of patient
	Not suitable for patients with intracranial hypertension	Greater cost
	No removal of cytokines	

Improved AKI risk stratification techniques need to be developed as they may be used to better inform timing decisions for RRT initiation and AKI therapeutics. Several AKI risk prediction scores and kidney-specific scoring models have been developed and validated in the setting of cardiac surgery; however most of these scores fail to predict milder form of AKI. Many novel AKI risk assessment techniques have been developed over the past 5 – 10 years including Renal Angina Index, functional and damage biomarkers, and the furosemide stress test; (FST) however these methods still require large scale validation. Appropriate dosing of medications, especially antibiotics remains challenging as the pharmacokinetic depends not only on the type of filter, frequency, and duration of PIRRT but also on the timing of drug administration in relation to the prolonged therapy. Standardization of terminology and establishment of prescription guidelines may lead to increased utilization of this modality of renal replacement therapy.

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DIALYSIS THERAPY FOR ICU

Who needs dialysis? Guidelines for the initiation of renal replacement therapy

- Severe hyperkalaemia, unresponsive to medical therapy
- Fluid overload with pulmonary oedema (in the context of acute renal failure)
- Uraemia (blood urea >30–50 mmol/l)
- Complications of severe uraemia: encephalopathy, pericarditis, neuropathy/myopathy
- Severe acidosis (pH <7.1)
- Drug overdose with a dialyzable toxin :

Controlled, predictable correction of electrolytes and acid base derangements is feasible with continuous renal replacement therapy (CRRT). Eliminating CRRT system downtime and declining dialyzer performance preferably with regional citrate anticoagulation may enhance our ability to apply simplified kinetic modeling to the CRRT control of select solutes, for example, sodium and bicarbonate. CRRT can mitigate and thereby mask profound pathophysiologic process that are disturbing the electrolytes and acid base balance. Embracing a kinetic analytical approach to the understanding of solute fluxes during CRRT allows for the prompt recognition of pathologic conditions such as ongoing tissue breakdown and ischemia. Prolonged intermittent renal replacement therapy (PIRRT) provides safe and cost-effective renal support to critically ill patients with acute kidney injury. There is significant heterogeneity among institutions in the delivery of PIRRT, with regard to technology, prescription and anticoagulation.Prolonged intermittent renal replacement therapy (PIRRT) provides safe and cost effective renal support to critically ill patients with acute kidney injury.

Intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) have been the mainstay of renal support for critically ill patients with AKI. Hybrid therapies for an extended period but on intermittent

basis, are becoming more popular to provide safe and cost effective are RT. There is significant heterogeneity among institutions in the delivery of prolonged intermittent renal replacement therapy(PIRRT), with regard to technology, prescription and anticoagulation. Appropriate dosing of medications, especially antibiotics, remains challenging as the pharmacokinetics depends not only on the type of filter, frequency, and duration of PIRRT but also on the timing of drug administration in relation to the prolonged therapy. Standardization of terminology and establishment of prescription guidelines may lead to increased utilization of this modality of renal replacement therapy. The number of acute kidney injury (AKI) survivors is increasing rapidly due to the combined effects of population growth, a rising incidence of AKI, and improved short – term survival. AKI is associated with subsequent elevation in blood pressure, cardiovascular events, incident and progressive CKD, and mortality. Optimal care for AKI survivors is not well defined and will require understanding the long term implications of AKI, identifying patients at highest risk for these outcomes, and targeting modifiable risk factors for intervention. The cost of CRRT using extracorporeal therapy is prohibitive in India and meta analysis have shown minimal benefit in terms of survival in critically ill patients with AKI in ICU. If there are no contra indications in advocating continuous peritoneal dialysis serves as a cost effective and successful outcome as is our experience.

Whenever possible, drug level should be closely monitored to guide dosing. Nephrologist infectious disease physcicians and critical care physcicians work closely with a clinical pharmacist who is familiar with RRT modalities and clearance rates should develop drug dosing guide lines. Dialysis prescription may be individualized depending on the duration and/or severity of a specific disorder (Table 4).

Nutritional requirements vary in AKI patients in ICU depending on conservative or renal replacement therapy. A skilled renal dietician forms an important part of the team which makes decisions on a day today basis. As RRT will produce loss of essential nutrients including vitamins, micro and macro elements and amino acids appropriate replacement through enteral route with minimum of 30 to 35 kcal/kg is necessary.

With regard to best practices in the ICU early mobilization, including mobilization of patients on CRRT is associated with improved functional outcomes. Routine GI prophylaxis, in particular with proton pump inhibitors, is not recommended due to increased rates of C. difficle and concerns for interterstial nephritis. GI prophylaxis should there for only be considered in high risk patients, and H_2 blockers should be strongly considered as first line agents.

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