

# ISCCM Guidelines on Acute Kidney Injury and Renal Replacement Therapy

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## ABSTRACT

Acute kidney injury (AKI) is a complex syndrome with a high incidence and considerable morbidity in critically ill patients. Renal replacement therapy (RRT) remains the mainstay of treatment for AKI. There are at present multiple disparities in uniform definition, diagnosis, and prevention of AKI and timing of initiation, mode, optimal dose, and discontinuation of RRT that need to be addressed. The Indian Society of Critical Care Medicine (ISCCM) AKI and RRT guidelines aim to address the clinical issues pertaining to AKI and practices to be followed for RRT, which will aid the clinicians in their day-to-day management of ICU patients with AKI.

**Keywords:** Acute kidney injury, Biomarkers, Continuous renal replacement therapy (CRRT), ECMO, Guidelines, Renal replacement therapy.

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## INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome with organ cross-talk. It is a major issue in hospitalized patients, with incidence ranging from 1 to 7% of all hospitalized patients and from 30 to 50% of intensive care unit (ICU) patients.<sup>1</sup> Morbidity and mortality associated with AKI remain high, ranging from 20 to 60%, despite improvements in management strategies.<sup>2</sup> AKI can also lead to the development or progression of chronic kidney disease (CKD), proteinuria, and cardiovascular diseases. The best treatment of AKI is prevention with avoidance of nephrotoxic agents and hemodynamic optimization. Renal replacement therapy (RRT) remains the mainstay of treatment for severe AKI in ICU. There are at present multiple disparities in uniform definition, diagnosis, and other areas of AKI and RRT that need to be addressed.

## METHODOLOGY AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

The Indian Society of Critical Care Medicine (ISCCM) AKI Guidelines committee was formulated in June 2020 and included eminent professionals from the field of Critical Care Medicine and Nephrology drawn from across the country. The guideline development occurred through a series of virtual meetings held weekly by the working group members, defining the timeline and scope of the guidelines, discussing conflicts of interest, planning the literature search, and eventually formulating the recommendations for each topic with their gradings as per the GRADE methodology previously published.<sup>3</sup> The steering committee members undertook an extensive review of literature identifying major randomized control trials (RCTs), *Cochrane Reviews* and protocols via the Cochrane Collaboration website ([www.cochrane.org](http://www.cochrane.org)), and by searching standard databases—*MEDLINE*, *EMBASE*, *PUBMED*, and Cumulative Index using “systematic review” or “meta-analysis” as a publication type or

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text word in the title or abstract. Within each recommendation, the strength of recommendation is indicated as Level I (Strong Recommendation) and Level II (Weak Recommendation), and the quality of the supporting evidence is shown as A, B, C (Table 1).

The document has been divided into two sections: AKI with eight topics and RRT with 12 topics for recommendations.

AKI section includes:

- Controversies in AKI nomenclature
- Risk assessment
- Early recognition and management
- Diagnosis of AKI
- Drug dosing in AKI
- Nutrition in AKI
- AKI recovery

The RRT section includes:

- Modes of RRT
- Indications of RRT
- Timing of initiation
- RRT Hardware
- Dosing of RRT
- Monitoring during RRT
- Replacement fluids
- Anticoagulation
- RRT in dys-electrolytemia
- RRT in toxicology
- RRT with ECMO
- Weaning from RRT

### Scope of Guidelines

The guidelines for both AKI and RRT are relevant only to critically ill adult patients in ICU with AKI and do not apply to patients with CKD *per se*. The purpose of these guidelines is to help clinicians involved in the management of ICU patients with AKI and not to replace their clinical knowledge, experience, or skills. Adaptation of guidelines in individual ICUs may be approached as per available local resources and expertise. As the subject of AKI in ICU is ever evolving, these guidelines are subject to change from time to time.

**Table 1:** Grade recommendations

| <i>Grade of recommendation</i>                          | <i>Quality of supporting evidence</i>  |
|---|--|
| 1A.<br>Strong recommendation, high-quality evidence     | Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form.   |
| 1B.<br>Strong recommendation, moderate quality evidence | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. |
| 1C.<br>Strong recommendation, low-quality evidence      | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws.   |
| 2A.<br>Weak recommendation, high-quality evidence       | Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form.   |
| 2B.<br>Weak recommendation, moderate quality evidence   | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. |
| 2C.<br>Weak recommendation, low-quality evidence        | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws.   |
| UPP (Useful Practice Point)                             | Not backed by sufficient evidence; however, a consensus reached by the working group, based on clinical experience and expertise.  |

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## EXECUTIVE SUMMARY OF AKI AND RRT

### AKI Nomenclature, Definition, and Staging

The change in nomenclature from acute renal failure (ARF) to AKI signifies the substantial impact of even a mild decline in kidney function on morbidity and mortality. In June 2019, Kidney disease: improving global outcomes (KDIGO) held a Consensus Conference to standardize and refine the nomenclature to describe kidney function and disease and develop a common glossary for scientific publications.

#### Recommendations

- We recommend using the term AKI alone, to describe the sudden decline in kidney function in the critically ill (UPP).
- We recommend the use of KDIGO criteria to diagnose AKI in the ICU (1A).
- We recommend the staging of AKI according to KDIGO criteria (1A).

#### AKI Risk Stratification

All patients admitted to the ICU should be stratified based on their risk of developing AKI and progression to higher stages of AKI and the need for RRT. The risk factors for susceptibility to AKI

include advanced age, hypertension (HT), diabetes mellitus (DM), pre-existing CKD, burns, cardiac surgery, trauma causing rhabdomyolysis, volume depletion, fluid overload, nephrotoxic drugs and agents, sepsis, cardiac failure, persistent shock, and the use of vasopressors.

#### Recommendations

- We recommend that all patients admitted to the ICU be stratified based on their susceptibility to developing AKI (1B).

### AKI Prevention and Early Management

#### Early Recognition of Subclinical AKI

All critically ill patients should be monitored closely for early identification of subclinical AKI. Continuous and dynamic monitoring using specific clinical criteria and/or biomarkers should be used to identify subclinical AKI in the high-risk population. Careful attention should be given to reversible and treatable causes of AKI to initiate prompt corrective measures.

#### Recommendations

- We recommend that patients at an increased risk of AKI should be recognized early and managed and monitored using a custom-made clinical approach (UPP).
- We recommend the utilization of clinical tools to identify subclinical AKI and recognize the patients who are likely to benefit from early interventions to prevent AKI (1B).
- We suggest the use of computerized and or machine learning algorithms, wherever possible, that incorporate multiple risk factors for recognition of AKI, rather than a single criterion (2B).

#### Use of AKI Care Bundles

The AKI care bundle includes optimization of hemodynamics and volume status, hyperglycemia management, nephrotoxin stewardship, and in some cases, specialist consultation, such as a nephrologist.

#### Recommendations

- We recommend applying bundled care plan or intervention for all patients undergoing major surgery and cardiac surgery who are at risk of developing AKI (1B).
- We suggest using bundled care for all critically ill patients with early AKI (2B).

#### Hemodynamic Management

All critically ill patients, with AKI or at risk of developing AKI, should have individualized blood pressure targets with functional hemodynamic monitoring.

#### Recommendations

- We suggest functional and/or dynamic hemodynamic (HD) monitoring in patients with AKI (2A).
- We recommend the following blood pressure targets in critically ill patients to prevent AKI and progression of AKI.
  - Mean arterial pressure (MAP) >70–75 mm Hg (1B).
  - Diastolic blood pressure (DBP) >55 mm Hg (2B).
  - Mean perfusion pressure (MPP) >60 mm Hg (2B).
  - MAP >80–85 mm Hg in patients with chronic hypertension (1B).

#### Volume Optimization

Correction of hypovolemia is the mainstay of management of early AKI and prevention of further kidney injury. A restrictive fluid administration strategy is beneficial in preventing AKI progression. The crystalloid solutions are preferred for volume resuscitation.

#### Recommendations

- We recommend an individualized approach to volume expansion in the initial management of shock and hypovolemia be avoided (1A).
- We recommend the use of crystalloids for fluid resuscitation (1A).
- We recommend against the use of Starch for fluid resuscitation (1A).
- We suggest against the use of Gelatin or Dextrans for fluid resuscitation (2B).
- We suggest that the balanced salt solutions be preferred over 0.9% Saline in patients requiring large-volume resuscitation (2A).
- We suggest that if isotonic 0.9% saline (NS) is used for large-volume resuscitation, the patient should be monitored for the development of hyperchloremia (2B).

#### Use of Vasopressors

Norepinephrine is the preferred vasopressor to treat circulatory shock. Dopamine, Fenoldopam, and Levosimendan have no proven role in reno-protection. Terlipressin is emerging as the vasopressor of choice in patients with acute or chronic liver failure with the hepato-renal syndrome (HRS).

#### Recommendations

- We recommend norepinephrine over other vasopressors to achieve blood pressure targets in circulatory shock (1A).
- We recommend against the use of low-dose dopamine or fenoldopam for preventing AKI (1A).
- We suggest the use of terlipressin as a vasopressor of choice in patients with HRS (2B).

#### Glycemic Control

A blood glucose target of 180 mg/dL in critically ill patients is acceptable and beneficial in patients at risk of AKI.

#### Recommendations

- We recommend avoiding hyperglycemia, of blood glucose concentration above 180 mg/dL in patients at risk of AKI (1A).

#### Nephrotoxin Stewardship

Non-nephrotoxic or less nephrotoxic equivalents are preferred over nephrotoxic drugs wherever feasible. However, if a drug is essential it should not be withheld for a fear of developing AKI.

#### Recommendations

- We suggest against the use of nephrotoxic drugs and recommend less nephrotoxic drugs of the same class (2A).
- We recommend the monitoring of blood concentration of nephrotoxic drugs, if such a facility is available (2A).
- We suggest the use of strategies such as modification of drug interval or dose to limit nephrotoxicity, where a potentially nephrotoxic agent cannot be discontinued (2A).

### Peri-operative AKI Prevention

The optimization of hemodynamic status improves renal blood flow in the peri-operative period. The use of a statin in the peri-operative period is shown to reduce the risk of post-operative renal dysfunction in patients undergoing vascular and/or cardiac surgery.

#### Recommendations

- We suggest the use of statins in the peri-operative period in patients undergoing vascular or cardiac surgery to prevent AKI (2B).
- We recommend against the use of remote ischemic preconditioning (RIPC) to reduce the incidence of perioperative AKI (1B).

### Laboratory-based Diagnosis of AKI

Serum creatinine is by far the most widely used endogenous biomarker to assess kidney function and diagnose AKI. However, the major limitation of serum creatinine is being a late functional biomarker and being influenced by several nonrenal factors. Nevertheless, other biomarkers such as blood urea nitrogen to serum creatinine ratio (BUN/Cr), fractional excretion of sodium (FeNa), fractional excretion of urea (FeUrea), Urine Sodium concentration, urine specific gravity, and urine microscopy lack accuracy and consistency to diagnose AKI accurately, in critically ill patients.

A complete diagnostic work-up should be done to identify the etiology of AKI.

#### Recommendations

- We recommend a systematic diagnostic work-up to determine the etiology of AKI (UPP).

### Biomarkers in AKI

In the last couple of decades, several clinical studies have validated biomarkers for early diagnosis of AKI. Among the new biomarkers, Urine neutrophil gelatinase-associated lipocalin (NGAL) is widely studied and exhibits good accuracy to diagnose AKI early, and predict the severity and progression of AKI as well as mortality in critically ill patients.

#### Recommendations

- Urinary biomarkers for the early diagnosis of AKI:
  - We suggest measuring the urine NGAL and L-type fatty acid-binding protein (L-FABP) for early diagnosis of AKI (2B).
  - We recommend against the use of Urine Cystatin C for early diagnosis of AKI (UPP).
- Urinary biomarkers to predict AKI severity and mortality:
  - We suggest measuring urine NGAL to predict AKI severity and mortality (2C).
  - We recommend against the use of urine L-FABP and Cystatin C to predict AKI severity and mortality (UPP).

### Drug Dosing in AKI

Several factors influence the dosage of drugs in AKI including volume status, mode of administration (bolus vs infusion), and mode of RRT. A regular review of medications by an experienced clinical pharmacist is shown to reduce the incidence of adverse effects, errors in drug dosage, adverse drug interactions and drug incompatibilities. In case aminoglycosides are used they

should be used as a single daily dose for a minimal duration and the therapeutic drug level monitored if needed, to avoid nephrotoxicity.

#### Recommendations

- We suggest regular review of medications in ICU by a Clinical Pharmacist to reduce drug-related adverse events and dosing errors in patients with AKI (2B).
- We recommend against the use of aminoglycosides in patients with AKI if less nephrotoxic alternatives are available (1A).

### Nutrition in AKI

The nutritional requirements in patients with AKI vary widely and should be individualized based on the pre-existing nutritional status, catabolic rate, severity of AKI, underlying disease causing AKI, comorbidities, and the type and intensity of RRT. The protein requirements vary in AKI patients, depending on whether patients receive RRT or not and the mode of RRT.

#### Recommendations

- We recommend that ICU patients with AKI receive energy upto 25–30 kcal/kg/day, equivalent to 100–130% of resting energy expenditure (1A).
- We suggest the following protein intake in patients of AKI with critical illness:
  - Not on RRT: 1.3 g/kg/day up to 1.7 g/kg/day (2B).
  - On intermittent RRT: 1 g/kg/day up to 1.5 g/kg/day (2B).
  - On CRRT: up to 1.7 g/kg/day (2B).
- We recommend not to restrict the protein intake with renal insufficiency to avoid or delay initiating RRT (UPP).

### AKI Recovery and Follow-up

The goal of post-AKI monitoring is to mitigate the progression of AKI and reduce short-term and long-term complications by implementing timely and effective care protocols. Patients with AKI should be followed up with an AKI follow-up bundle. They should be categorized based on the risk of developing CKD.

#### Recommendations

- We recommend that all patients who survive an episode of AKI of any stage, be assessed at the end of 1 month of onset of AKI with AKI follow-up bundle and reviewed by a primary care physician or nephrologist (1B).
- We suggest that for long-term monitoring, the AKI follow-up bundle be performed by a physician or a nephrologist, once a year for category-1, and once in 6 months for category-2 patients (2C).
- We recommend that category-3 patients, who carry a high risk of progression to CKD and end-stage renal disease (ESRD), be followed up by a nephrologist from the time of hospital discharge, at an interval deemed necessary by the nephrologist (1B).

### Indications of RRT in AKI

RRT is used for several “renal” conditions in acute care settings which might be life-threatening or for “nonrenal” conditions like removal of cytokines in inflammatory states such as sepsis, removal of dialyzable poisons and toxins, and in cases of severe electrolyte disturbances resistant to medical treatment.

### Recommendations

- We recommend RRT for life-threatening conditions such as severe hyperkalemia, severe metabolic acidosis, fluid overload that are resistant to medical therapy causing severe cardiopulmonary compromise and other uremic complications that are unresponsive to medical therapy (1C).
- We recommend against the prophylactic use of RRT to prevent uremic complications (UPP).
- We recommend against prophylactic RRT for removal of contrast agent in patients with increased risk of contrast induced nephropathy (CIN) (1A).

### Timing of Initiation of RRT in AKI

The optimal time for starting RRT in AKI is subject to debate and controversy. Early initiation of RRT has theoretical advantages of prevention of severe electrolyte and acid–base imbalances, better volume management and prevention of uremic complications, but has not been shown to improve outcomes. A late initiation of RRT may avoid RRT induced kidney injury and may avoid RRT altogether in up to 50% of patients.

### Recommendations

- We recommend that RRT be initiated urgently in patients who meet one or more of the absolute indications (1A).
- For nonurgent indications we suggest RRT be considered when the capacity of the kidneys cannot meet the metabolic demands imposed by AKI on the body (UPP).

### Modality of RRT in AKI

A choice of several modalities of RRT for critically ill patients with AKI is available which are broadly classified as *continuous* and *intermittent* therapies. Several factors influence the choice of a mode of RRT in ICU:

- Patient-related factors like severity of critical illness, hemodynamic status, comorbidities, and organ dysfunction.
- Resource-related factors such as availability of RRT modality, clinician expertise and preference, technical support, and cost of therapy.

### Recommendations

- We suggest that the choice of RRT modality be based on the availability of the facility, experience, and expertise of medical staff and the clinical status of the patient (UPP).
- We recommend the use of continuous renal replacement therapy (CRRT) or sustained low efficiency dialysis (SLED) rather than intermittent hemodialysis (IHD) in patients who are hemodynamically unstable and may have intolerance to fluid removal (1B).
- We recommend IHD for rapid correction of lifethreatening hyperkalemia with cardiac arrhythmias (1B).
- We suggest the use of IHD or SLED over CRRT and peritoneal dialysis (PD) for rapid correction of metabolic acidosis (2C).
- We recommend CRRT over IHD or SLED in patients with acute brain injury or increased intracranial tension (1B).
- We suggest the use of CRRT, SLED, or IHD over PD, for hypercatabolic patients (2C).

### RRT Hardware

Vascular access is a major determinant of circuit life span during RRT. The double-lumen nontunneled dialysis catheters are preferred due

to ease of insertion. The biocompatible cellulose membranes have shown a survival advantage over the bio-incompatible membranes and are hence preferred.

### Recommendations

#### Catheters

- We suggest using nontunneled dialysis catheter in the critically ill patients who are expected to receive RRT for a short duration (2B).
- We recommend the use of double lumen catheters over triple lumen or single lumen catheters (UPP).
- We recommend the use of ultrasonography (USG) guidance for the insertion of vascular access by trained personnel when available (1A).
- We recommend that the position of dialysis catheter inserted in the internal jugular and subclavian veins be confirmed radiologically (1A).
- We recommend internal jugular vein (IJV) preferably right IJV as the first choice for vascular access followed by the femoral veins. The subclavian veins are the least preferred sites for dialysis catheter (1A).
- We recommend against antibiotic prophylaxis prior to catheter insertion (1A).
- We recommend against regular timed change of dialysis catheters unless it is blocked or shows signs of infection (1B).

#### Dialysate membranes

- We recommend the use of biocompatible membranes for hemodialysis in patients with AKI (1A).

### Monitoring during RRT

The monitoring of RRT helps to ensure the delivery of prescribed RRT and prevent complications related to RRT to ensure safe delivery of the therapy. It is desirable to have standardized protocols for RRT monitoring that would aid the quality, efficacy, and safety of RRT.

### Recommendations

- We recommend a protocol-based template for prescribing and monitoring RRT and detailed documentation of the treatment (UPP).
- We recommend monitoring patient-related factors (hemodynamics, vasopressor dose, volume status, temperature and level of sensorium during RRT) and blood tests to monitor biochemical parameters tailored as per the individual need of the patient (UPP).
- We suggest monitoring the delivered dose of RRT (2C).

### Dose of CRRT in AKI

A dynamic rather than a fixed dose of RRT would be useful to meet the metabolic demands in AKI which may change with time during the illness. Studies indicate that an effluent volume of 20–25 mL/kg/minute is adequate for patients of AKI. A higher intensity or dose of RRT has no survival benefit and may be associated with increased incidence of RRT-related complications.

### Recommendations

- We recommend an individualized and prescribed dose of RRT, signed by an intensivist or nephrologist before the start of each session (UPP).

- We recommend that RRT prescription be assessed and revised from time to time till the optimal goal of therapy is achieved (UPP).
- We recommend a delivered dose of CRRT of 20–25 mL/kg/hour of effluent volume (1A).
- We recommend against using a high intensity or intensive dose of CRRT (1A).
- We suggest that the predilution factor be taken into consideration while prescribing CRRT to prevent under delivery of the dose (UPP).

### Replacement Fluids for CRRT

The choice of fluids for CRRT depends on acid-base balance, electrolyte and divalent ion balance, and degree of organ dysfunction. The bicarbonate and lactate-based solutions are similar in correcting metabolic acidosis but bicarbonate-based buffer solutions result in better hemodynamic stability. The custom-made solutions involve admixture of multiple intravenous fluids and carry a risk of compounding error and a break in sterility and hence commercial solutions specifically made for CRRT are preferred.

#### Recommendations

- We recommend bicarbonate-based fluids over the lactate-based fluids for dialysis and replacement in CRRT (1B).
- We suggest against the use of custom-made fluids for replacement in CRRT (UPP).

### Anticoagulation during RRT

Anticoagulation is required to prevent clotting of the extracorporeal circuit during RRT. RRT may be feasible without anticoagulation for short duration intermittent RRT and in the presence of impaired coagulation, dilutional coagulopathy, or thrombocytopenia. Regional Citrate Anticoagulation (RCA) is devoid of systemic effects with reduced risk of bleeding complications and hence better suited for CRRT in ICU. However, RCA for CRRT is complex and mandates a protocolized approach.

#### Recommendations

- We recommend anticoagulant therapy in AKI patients requiring RRT if there is no increased risk of bleeding. The patients who are on systemic anticoagulation do not usually require additional anticoagulation during RRT (1B).
- In patients with no clotting abnormalities, with no increased risk of bleeding, we recommend unfractionated heparin during intermittent modalities of RRT. In the case of CRRT, we recommend RCA in centers with adequate expertise and experience with this strategy; and in centers lacking the expertise and experience for RCA, anticoagulation with unfractionated heparin may be carried out (1B).
- In patients with impaired coagulation or increased risk of bleeding we suggest either no anticoagulation or RCA during CRRT, an anticoagulant-free strategy for intermittent RRT (2C).
- We recommend the following options for anticoagulation in heparin-induced thrombocytopenia (HIT): Direct thrombin inhibitors, including Argatroban and Factor Xa inhibitors, such as Danaparoid or Fondaparinux (1A).

### RRT for Dyselectrolytemia

The modality of RRT to correct electrolyte abnormalities is chosen based on their operational characteristics to suit the clinical

scenario. A rapid correction is best achieved with high-efficiency RRT such as IHD and SLED whereas more sustained correction is better achieved with CRRT.

#### Recommendations

- We recommend a high-efficiency RRT modality such as IHD or SLED when a rapid correction of electrolytes is needed in life-threatening emergencies (1B).
- We recommend that while RRT is performed the rate of correction of chronic hypo and hypernatremia should not exceed the recommended rate of correction. Serum Sodium can be corrected rapidly in acute symptomatic dysnatremia (1A).
- We suggest using RRT for the management of severe dysnatremia refractory to medical treatment whether with or without AKI (UPP).

### RRT in Toxicology

IHD which removes solutes and toxins by diffusion is the most widely utilized RRT worldwide for toxin removal. The use of CRRT has gained more acceptance in recent years in patients with hemodynamic instability and those with large molecular weight toxins which are more efficiently removed in CRRT by the process of convection. There is abundant clinical experience to support the utilization of RRT for toxic Alcohol poisoning, Salicylate toxicity, Lithium overdose, Metformin, and Valproic acid toxicity.

#### Recommendations

- We recommend against the routine use of RRT based only on the dose of ingested toxin or serum drug level in the absence of signs of toxicity. RRT should be initiated where the benefit outweighs the risk of the procedure and associated cost (1C).
- We suggest discontinuing RRT upon clinical improvement and resolution of manifestations of toxicity (2C).
- We recommend IHD as the modality of choice for most dialysable toxins (1C).

### Weaning from RRT

Weaning from RRT is desirable to prevent dialysis-related complications, reduce the cost of hospitalization, and prevent delay in renal recovery. Decision to wean acute RRT is complex and multidimensional; integrating several clinical, laboratory, and resource factors.

#### Recommendations

- We recommend that weaning from RRT may be considered in AKI when the intrinsic capacity of the kidneys has increased to a degree sufficient enough to cope with the metabolic and fluid demands (UPP).
- We recommend that spontaneous improvement in urine output from oliguric to nonoliguric state (UO >400 mL/day) or urine creatinine clearance of more than 15–20 mL/minute may be considered as the reliable clinical parameters to consider weaning from RRT (1B).
- We suggest that withdrawal from RRT may be considered in case the deteriorating condition renders the continuation of RRT to be futile after a comprehensive deliberation with all involved in the care of the patient and family (UPP).

### RRT and ECMO

Around 25–68% of ECMO-treated patients need RRT for AKI. Usually, the patients on ECMO are hemodynamically fragile and hence a

continuous mode that permits a slow and steady solute and water clearance may be preferred. Out of the three main modalities of combining CRRT and ECMO: the parallel system, the in-line hemofilter technique, and the integrated system; none has been found to have superiority over the others.

### Recommendations

- We suggest combining the use of RRT with ECMO in patients on ECMO having AKI, with CRRT as the preferred mode for RRT (UPP).
- We recommend an individualized approach with close monitoring of fluid and metabolic status for timely initiation of RRT with ECMO (UPP).
- We recommend against one technique over another (Integrated vs parallel system) for CRRT on ECMO and the choice should be based on local expertise and human resources (UPP).

## GUIDELINES—ACUTE KIDNEY INJURY

### Introduction

AKI is a major health issue in hospitalized patients, occurring in up to 30–50% of ICU patients. There exist multiple disparities in uniform definition, diagnosis, and other arenas of AKI that need to be defined. The guidelines committee tried to define certain areas of AKI which are of utmost clinical importance.

### AKI Nomenclature, Definition and Staging

- We recommend using the term AKI alone, to describe the sudden decline in kidney function in the critically ill (UPP).
- We recommend the use of KDIGO criteria to diagnose AKI in the ICU (1A) (Table 2).
- We recommend the staging of AKI according to KDIGO criteria (1A) (Table 3).

### Rationale

The change in nomenclature from ARF to AKI, to describe a condition of an acute decline in kidney function, signifies the clinical recognition of the substantial impact of even a small decline in renal function on the morbidity and mortality in critically ill patients. In

**Table 2:** Acute kidney injury (AKI) definition as per KDIGO

| <i>AKI is defined as any of the following</i>   |  |
|---|--|
| • Increase in SCr by $\geq 0.3$ mg/dL ( $\geq 26.5$ $\mu\text{mol/l}$ ) within 48 hours; or                             |  |
| • Increase in SCr to $\geq 1.5$ times baseline, which is known or presumed to have occurred within the prior 7 days; or |  |
| • Urine volume $< 0.5$ mL/kg/hour for 6 hours.  |  |

**Table 3:** Staging of acute kidney injury (AKI)

| Stage | Serum creatinine  | Urine output   |
|-------|---|--|
| I     | 1.5–1.9 times baseline OR $\geq 0.3$ mg/dL ( $\geq 26.5$ mmol/L) increase   | $< 0.5$ mL/kg/hour for 6–12 hours                                    |
| II    | 2.0–2.9 times baseline  | $< 0.5$ mL/kg/hour for $\geq 12$ hours                               |
| III   | 3.0 times baseline OR Increase in serum creatinine to $\geq 4.0$ mg/dL ( $\geq 353.6$ mmol/L) OR Initiation of renal replacement therapy OR, In patients $< 18$ years, decrease in eGFR to $< 35$ mL/minute per $1.73$ m <sup>2</sup> | $< 0.3$ mL/kg/hour for $\geq 24$ hours OR Anuria for $\geq 12$ hours |

June 2019, Kidney Disease: Improving Global Outcomes (KDIGO) conducted a Consensus Conference to standardize and refine the nomenclature to describe kidney function and disease and developed a glossary that could be uniformly used in scientific publications.<sup>4</sup> They recommended the use of “kidney” rather than “renal” or “nephro” when referring to kidney disease and kidney function, the term which is easily understood by patients.

Before 2004, the definition of AKI in the literature varied widely which rendered the comparison of studies in AKI difficult. This drawback was addressed when the Acute Dialysis Quality Initiative (ADQI) Group published their landmark consensus definition of AKI in adults in 2004, the Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) classification consisting of five stages of AKI<sup>5</sup> which was further modified in 2007 by the AKI Network (AKIN), to improve its sensitivity.<sup>6</sup> Risk, Injury, and Failure were now staged I, II, and III, respectively, and a rise in serum creatinine  $\geq 0.3$  mg/dL within 48 hours was included in stage I, recognizing that even a small increase in serum creatinine significantly increases the mortality, length of hospital stay, and cost of hospitalization.<sup>7</sup> The GFR criterion was withdrawn as a parameter to define AKI. Loss and end-stage kidney disease were removed as they were considered as outcomes and not the stages of AKI. AKIN criteria also stipulated that the definition be applied only after achieving adequate hydration status and excluding urinary obstruction. In addition, patients who were initiated on RRT were classified as stage III, regardless of their serum creatinine and urine output at RRT initiation. In 2012 the KDIGO-AKI workgroup merged RIFLE and AKIN and formed the KDIGO definition for AKI (Table 2), which defined AKI as an increase in serum creatinine by  $\geq 0.3$  mg/dL within 48 hours or a rise in creatinine to  $\geq 1.5$  times baseline within the last 7 days.<sup>8</sup> The urine output criteria remained the same in all three definitions.

Several studies have shown the superiority of the KDIGO definition over the AKIN and RIFLE criteria. A prospective, multicenter observational study compared these three definitions analyzing the database of 3,107 ICU patients with AKI.<sup>9</sup> They found that the KDIGO definition had a higher sensitivity for AKI diagnosis, compared to RIFLE or AKIN criteria was a better predictor of hospital mortality, compared to RIFLE, but similar to AKIN.

A 2015 systematic review and meta-analysis comparing RIFLE vs AKIN criteria in critically ill patients showed that the AKIN criteria could identify more patients in AKI compared to RIFLE but did not show a better ability in predicting hospital mortality.<sup>10</sup> A retrospective single-center cohort study of 31,970 hospitalizations showed that AKI incidence was the highest according to the KDIGO definition followed by the AKIN and RIFLE.<sup>11</sup>

### AKI Risk Stratification

- We recommend that all patients admitted to the ICU be stratified based on their susceptibility to developing AKI (1B).

### Rationale

Risk stratification of patients allows for making systematic care management decisions, with an intent to provide greater attention and resources to patients in higher risk levels.

A large multinational study showed that increasing severity of AKI was associated with higher mortality.<sup>12</sup> Several studies have shown a strong association between a more severe degree of AKI and adverse hospital outcomes including mortality during and after hospitalization and future development of CKD.<sup>13–15</sup> Analysis of Taiwan National Health Insurance (NHI) database showed an

independent association of dialysis-requiring AKI with future coronary events.<sup>16</sup> Early identification of kidney injury provides an opportunity to apply interventions such as removal of the cause of injury, avoidance of nephrotoxic drugs, optimization of hydration and hemodynamics, to limit the progression of AKI.

Every patient admitted to the ICU should be stratified for the risk of developing AKI, and the risk of progression to higher stages of AKI or the need for RRT.

The common clinical risk factors for developing AKI in a critically ill patient are:

- Advanced age >75 years
- Comorbid conditions such as HT, DM, CKD, burns, cardiac surgery, cancer, heart failure, organ transplant
- Exposures include volume depletion, nephrotoxins (Vancomycin, RAAS Blockers, Aminoglycosides, Amphotericin, intravenous (IV) contrast), and sepsis
- Clinical and laboratory parameters: reduced urine output, large cumulative positive fluid balance, and progressive increase in serum creatinine
- Clinical findings: Hypotension, cold extremities, prolonged capillary refill time

Sepsis, hypovolemia, hypoalbuminemia, cardio-renal syndrome, and obstructive uropathy have been identified as the common causes for severe AKI in observational studies and meta-analyses.<sup>17–19</sup> A 2020 meta-analysis of 39 studies with 168,740 patients showed that every 1.0 g/dL decrease in serum albumin was associated with a 1.685 times higher risk of AKI.<sup>19</sup>

An observational study of 3,333 patients with AKI, identified a change in serum creatinine  $\geq 148$   $\mu\text{mol/L}$  (1.67 mg/dL) from baseline as a good predictor of the need for RRT.<sup>20</sup>

#### Risk Factors in Specific Conditions

- **Sepsis:** Septic shock is the commonest cause of AKI in critically ill patients, with specific risk factors being gram-negative infections, abdominal infection, administration of vasopressors and vasoactive drugs, mechanical ventilation, positive blood cultures, and organ transplantation.<sup>18</sup> A higher need for RRT has been reported in patients with septic AKI, compared to nonseptic AKI.<sup>18</sup>
- **Contrast-induced nephropathy (CIN):** The patient-related risk factors for CIN are the pre-existing CKD, low GFR, albuminuria, DM, low effective circulating blood volume, concomitant use of other nephrotoxic agents such as NSAIDs, and the procedure-related risk factors are higher contrast volume, use of hyperosmolar contrast agent, and intraarterial administration of the contrast agent.<sup>21</sup>
- **Burns:** Independent risk factors for AKI in patients with burns are the percentage of the total body surface area (TBSA%), full-thickness TBSA%, abbreviated burn severity index on admission, and rhabdomyolysis. Other recognized risk factors are inhalation injury, mechanical ventilation, and cardiovascular complications.<sup>22</sup>
- **Postoperative AKI:** In surgical patients, a significant association has been found between emergency surgery, intra-peritoneal surgery, duration of surgery, elevated C-reactive protein (CRP), blood transfusions, reduced pre-operative estimated GFR, and AKI risk. A large study reported a direct correlation between the severity and duration of intraoperative hypotension and the development of AKI.<sup>23</sup>

- **Postoperative cardiac surgery:** A meta-analysis published in 2019 showed a strong association between the duration of low oxygen delivery during cardiopulmonary bypass, on-pump surgery, transfusion of more than one unit of red blood cells, and development of AKI perioperatively after major cardiac or vascular surgery.<sup>24</sup> Preoperative use of aldosterone antagonist was associated with a lower risk of AKI in patients undergoing cardiac surgery.<sup>25</sup> Preoperative serum brain natriuretic peptide levels and low albumin concentration are associated with the need for RRT after off-pump coronary artery bypass graft (CABG) surgery.<sup>26</sup>

- **Acute liver failure (ALF):** The specific risk factors of AKI in patients with ALF are the severity of ALF, and ALF due to acetaminophen poisoning.

Multiple AKI risk prediction models and AKI risk prediction scores have been evaluated and validated in clinical trials, with a combination of various risk factors; however, none of them can be recommended for use in any specific population of patients.

## AKI Prevention and Early Management

### Early Recognition

- We recommend that patients at an increased risk of AKI should be recognized early, monitored and managed using a custom-made clinical approach (UPP).
- We recommend the utilization of clinical tools to identify subclinical AKI and recognize the patients who are likely to benefit from early interventions to prevent AKI (1B).
- We suggest the use of computerized and or machine learning algorithms that incorporate multiple risk factors for recognition of AKI, rather than a single criterion (2B).

### Use of AKI Care Bundles

- We recommend the application of bundled care plan or intervention for all patients undergoing major surgery and cardiac surgery who are at risk of developing AKI (1B).
- We suggest using bundled care for all critically ill patients with early AKI (2B).

### Hemodynamic Monitoring

- We suggest functional and/or dynamic hemodynamic (HD) monitoring in patients with early AKI (2A).
- We recommend the following blood pressure targets in critically ill patients to prevent AKI and progression of AKI.
  - MAP >70–75 mm Hg (1B).
  - DBP >55 mm Hg (2B).
  - MPP >60 mm Hg (2B).
  - MAP >80–85 mm Hg in patients with chronic hypertension (1B).

### Volume Optimization

- We recommend an individualized approach to volume expansion in the initial management of shock; hypervolemia be avoided (1A).
- We recommend the use of crystalloids for fluid resuscitation (1A).
- We recommend against the use of starch for fluid resuscitation (1A).
- We suggest against the use of gelatin or dextrans for fluid resuscitation (2B).

- We suggest that the balanced salt solutions be preferred over 0.9% saline in patients requiring large-volume resuscitation (2A).
- We suggest that if isotonic 0.9% saline (NS) is used for large-volume resuscitation, the patient be monitored for the development of hyperchloremia (2B).

#### Vasopressor Use

- We recommend norepinephrine over other vasopressors to achieve blood pressure targets in circulatory shock (1A).
- We recommend against the use of low-dose Dopamine or Fenoldopam for preventing AKI (1A).
- We suggest the use of Terlipressin as a vasopressor of choice in patients with HRS (2B).

#### Hyperglycemia

- We recommend avoiding hyperglycemia, of blood glucose concentration above 180 mg/dL in patients at risk of AKI (1A).

#### Nephrotoxins

- We suggest against the use of nephrotoxic drugs and recommend less nephrotoxic drugs of the same class (2A).
- We recommend monitoring blood concentrations of nephrotoxic drugs, if such a facility is available (2A).
- We suggest the use of strategies such as modification of drug interval or dose to limit nephrotoxicity, where a potentially nephrotoxic agent cannot be discontinued (2A).

#### Prevention of Perioperative AKI

- We suggest the use of statins in the perioperative period in patients undergoing vascular or cardiac surgery to prevent AKI (2B).
- We recommend against the use of RIPC to reduce the incidence of perioperative AKI (1B).

#### Rationale

- **Early recognition of subclinical AKI:** Critically ill patients with an increased risk of developing AKI should be subjected to continuous and dynamic monitoring using the clinical and biochemical parameters to identify subclinical AKI. They should be closely and carefully observed for the impact of preventive measures by monitoring metabolic parameters, diuresis, cumulative fluid balance, and biomarkers. Continuous minute-to-minute monitoring of urine output in real time may enable rapid therapeutic interventions and can be incorporated into patient data systems to improve management.<sup>27</sup> Literature has established intraabdominal hypertension as an independent cause of renal impairment in critically ill patients.<sup>28</sup> Measurement of intraabdominal pressure in patients at high risk can also help in earlier recognition of AKI.

Studies have shown that interventions that improve recognition of AKI and initiation of prompt early supportive care might improve survival and reduce the length of hospital stay, as reported in a large observational study of more than 60,000 patients.<sup>29</sup> However, a meta-analysis published in 2017 failed to detect any change in the care process and improvement in patient outcome, with the implementation of AKI e-alerts.<sup>30</sup>

- **Use of AKI care bundles:** Bundled care for AKI includes optimization of hemodynamics and volume status, hyperglycemia management, nephrotoxin stewardship, and in some cases, specialist consultation such as with a nephrologist. Several studies have assessed the role of bundled care for

patients with or at risk of AKI. In a study involving 276 cardiac surgery patients with elevated AKI biomarkers, preventive bundled protocol significantly reduced the incidence of postoperative AKI (ARR 17%,  $p=0.04$ ) compared to standard care.<sup>31</sup> Another recent pragmatic randomized trial of 24,051 AKI episodes showed that a multifaceted intervention with AKI care bundles based on AKI alerts did not reduce 30-day AKI mortality but resulted in reductions in the length of hospital stay.<sup>32</sup>

- **Hemodynamic management:** The blood pressure targets should be individualized for critically ill patients at risk of developing AKI or already having AKI. In a study of patients undergoing cardiac surgery, the titration of norepinephrine to achieve a MAP of 75 mm Hg from 60 mm Hg showed improved GFR and renal oxygen delivery.<sup>33</sup> A prospective study of 217 patients concluded that the optimal MAP to prevent AKI at 72 hours was between 72 and 82 mm Hg.<sup>34</sup> In a retrospective analysis of 276 patients with sepsis, a higher MAP was required to maintain kidney function and a decline in MAP to below 75 mm Hg predicted the need for RRT.<sup>35</sup>

Diastolic arterial pressure (DAP) also has an impact on the development of AKI. A small observational study of 137 septic patients found no association with MAP but found that patients with new AKI or persistent AKI had a lower DAP (54.8 vs 51.5 mm Hg).<sup>36</sup>

Maintaining higher MAP in patients with pre-existing hypertension reduces the incidence of AKI. In a multicenter RCT, 777 septic patients were randomized to MAP targets of 65–70 or 80–85 mm Hg. In patients with chronic hypertension randomized to a higher MAP had a lower incidence of AKI.<sup>37</sup>

- **Volume optimization:** Correction of hypovolemia is the mainstay of management of early AKI, to prevent further injury. However, overzealous fluid administration may cause harm. A restrictive fluid strategy after an initial resuscitation is shown to reduce the progression of AKI.<sup>38</sup>

There is no single method of assessing fluid responsiveness which is superior; hence multiple clinical assessments and measurements should be done periodically. In patients who do not respond to volume expansion, vasopressors should be added early to achieve the hemodynamic targets.

The choice of fluid for volume resuscitation remains debatable. Among crystalloids, the use of 0.9% saline or Lactated Ringer showed no difference in the incidence of AKI or the need for RRT.<sup>39</sup> Large RCTs have shown a higher need for RRT with HES than with crystalloid solutions. A 2018 Cochrane review of 28 RCTs concluded that the starch-based fluids increase the risk of RRT initiation.<sup>40</sup>

The observational data suggest that administration of Gelatin and Dextran solutions contributes to osmotic nephrosis induced AKI in critically ill patients and also following major surgery.<sup>41</sup>

Albumin administration is relatively safe, but there is no definitive evidence that it limits the progression of AKI. Intravenous 4% Albumin administration showed no renal benefit in the SAFE trial, but lesser volume for resuscitation was needed.<sup>42</sup>

Yunos et al. showed a lower incidence of AKI and RRT in a group resuscitated with chloride restrictive intravenous fluids.<sup>43</sup> The SPLIT study, mainly involving post-operative patient's resuscitation with median volumes of 2.0 L, showed no difference in the incidence of AKI and RRT between NS and balanced solution.<sup>44</sup> SMART study of 15,802 patients with sepsis showed that the use of NS increased the need for RRT compared to balanced crystalloids when used in large volume for fluid resuscitation.<sup>45</sup> A 2015 systematic review of 6,253 patients showed that postoperative fluid resuscitation with balanced crystalloids reduced the incidence of AKI when compared

to isotonic saline.<sup>46</sup> Thus, when large volumes of resuscitation are required, balanced solutions may be preferred over 0.9% saline.

The question about AKI and its response to diuretics is still begging to be answered. A meta-analysis published in 2019 showed no association between furosemide administration and mortality or the need for RRT in AKI.<sup>47</sup> Another meta-analysis published in 2020 concluded that a furosemide stress test accurately predicted new AKI development and AKI progression.<sup>48</sup> Furosemide and other loop diuretics commonly used in oliguric AKI in clinical practice have failed to show any benefit to improve renal function. Clinical trials have failed to prove the role of furosemide in shortening the duration of AKI or reduce the need for RRT.<sup>49</sup>

- **Use of vasopressors and inotropes:** Norepinephrine is the vasopressor of choice in patients in vasodilatory shock. Even in cardiogenic shock, norepinephrine has been associated with superior survival with a trend towards more RRT-free days.<sup>50</sup> Vasopressin has a role in the management of norepinephrine refractory shock, and in a subgroup analysis of patients with shock, vasopressin was shown to reduce the progression of stage I AKI to higher stages.<sup>51</sup>

Low-dose dopamine was widely used in the past for renal protection. However, a meta-analysis published in 2005 showed no benefits and, on the contrary, found it to be potentially harmful.<sup>52</sup> Fenoldopam, a pure Dopamine-1 receptor agonist, and Levosimendan, a calcium sensitizer, so far, have shown no role in renal protection.

In an open-label RCT of 120 acute on chronic liver failure patients with HRS, the use of Terlipressin as compared to noradrenaline resulted in higher rates of reversal of HRS and a significant reduction in the need for RRT.<sup>53</sup>

- **Glycemic control:** Tight glycemic control is frequently used in patients at risk of AKI and those who develop AKI. Thomas et al. in a 2007 systematic review of randomized trials of tight glycemic control in 2,864 critically ill patients found a 38% risk reduction of AKI and a nonsignificant trend toward reduction in the need for RRT.<sup>54</sup> Tight glucose control is challenging in clinical practice and carries a risk of hypoglycaemic episodes. Hence a blood glucose target of <180 mg/dL in critically ill patients at risk of AKI is acceptable and beneficial.
- **Nephrotoxin stewardship:** Common nephrotoxic drugs used in ICU are aminoglycosides, nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), amphotericin B, iodinated contrast, vancomycin, and polymyxins. Nephrotoxin stewardship prioritizes the evaluation and appropriateness of nephrotoxin exposure, rather than discontinuation of all nephrotoxins. When administration of nephrotoxic drug is essential, cumulative nephrotoxin burden must be considered. Wherever possible, nephrotoxic drugs like ACEI or ARBs should be replaced by non-nephrotoxic or less nephrotoxic equivalents.<sup>55</sup> However, if any drug is essential for patient management, it should not be withheld just because of its nephrotoxicity. In addition, certain risk-reduction strategies to reduce nephrotoxin exposures could be implemented (e.g., once-daily aminoglycoside dosing). Though NSAIDs are generally considered as highly nephrotoxic, a 2018 Cochrane meta-analysis of 26 RCTs and quasi-RCTs, with 8,835 participants, showed an uncertain effect of NSAIDs use on the risk of developing post-operative AKI.<sup>56</sup> A recent meta-analysis and systematic review reported an incidence of AKI of 32% with colistin. However, most cases of AKI were mild and reversible with no increased risk of mortality or the need for RRT.<sup>57</sup>

In any patient requiring IV contrast administration, the risk for CIN should be weighed against the risk of not performing this diagnostic procedure. In patients with AKI who require contrast study, the benefits of the study should be weighed against the potential harm to the kidneys and in case of gadolinium use, likely risk of developing nephrogenic systemic sclerosis should be taken into account.<sup>58</sup> In a study of 3,485 septic AKI patients, the use of contrast agent did not increase RRT duration or RRT dependence.<sup>59</sup> The use of a low or iso-osmolar contrast agent, minimizing the contrast volume, has been found to reduce the risk of CIN. Administration of isotonic fluid administration is a time-tested intervention in the prevention of CIN. Normal saline is the currently recommended fluid for hydration, and a 2020 meta-analysis that included over 60 RCTs with 21,293 patients highlighted the role of hemodynamic guided hydration in the prevention of CIN.<sup>60</sup> The conflicting AMACING trial result of no difference in the incidence of CIN between the hydration and control groups has several reasons for it. This trial enrolled only 660 patients as against 1,300 planned initially and had a very low number of intra-arterial interventions.<sup>61</sup> A large RCT showed no benefit with isotonic bicarbonate solution or N-acetyl cysteine (NAC) administration in reduction of the need for RRT or 50% reduction in GFR at 90 days, following angiography.<sup>62</sup> However, the use of NAC and Statin pre-treatment has been found to reduce the incidence of CIN in two meta-analyses published in 2020.<sup>63,64</sup> Based on the current evidence, no conclusive recommendations apart from ensuring euolemia can be made for CIN prevention.

- **Perioperative AKI prevention:** Hemodynamic optimization to optimize renal blood flow during the peri-operative period is a time-proven method to prevent AKI in the perioperative period.

The analysis of 18 studies consisting of 32,747 patients undergoing CABG surgery showed a significant protective effect of preoperative Statin therapy for perioperative renal dysfunction and requirement for RRT.<sup>65</sup>

A 2019 meta-analysis concluded that RIPC did not reduce the incidence of AKI following cardiac surgery with CPB.<sup>66</sup> Another systematic review and meta-analysis in 2020 showed no benefit with the use of frusemide in reducing the postoperative AKI.<sup>67</sup>

#### Laboratory-based Diagnosis of AKI

- We recommend a systematic diagnostic work-up to determine the etiology of AKI (UPP).

#### Rationale

The diagnosis of AKI is traditionally based on urine output and serum creatinine despite its limitations and the growing interest in novel biomarkers.<sup>8,68</sup> To date, no other endogenous marker has been evaluated and used as widely as serum creatinine in assessing AKI, and currently, there is no role for exogenous markers such as iohexol or iothalamate in assessing kidney function in the clinical setting. The major limitation of serum creatinine is that it only assesses the excretory function of the kidney, increases only after a substantial reduction in GFR, and is affected by several nonrenal factors such as volume status, muscle mass, drugs, and dietary patterns. The lack of a "steady-state" in critically ill patients renders the creatinine-based GFR estimation redundant. Very few trials have sought to study the correlation between the various eGFR techniques and 24-hour urine creatinine clearance in the ICUs, and the results are conflicting. The limited available evidence suggests that measuring urine creatinine clearance over at least 8-hours as opposed to shorter durations is useful in measuring GFR in patients with AKI.<sup>69</sup> Among the equations used to estimate GFR, MDRD-6 and

modified Jelliffe's equations fared relatively better.<sup>70</sup> Currently, there is growing interest in the application of the concept of "Kinetic GFR" which takes into account the dynamic changes in GFR in critically ill patients.<sup>70</sup> Despite the limitations, creatinine-based diagnosis and classification of AKI have brought about standardization both in clinical and research front and have shown a strong association with patient-centered outcomes.<sup>2</sup>

Other biochemical measurements such as blood urea nitrogen (BUN)/Creatinine ratio, fractional excretion of sodium (FeNa), fractional excretion of Urea (FeUrea), urine specific gravity, and urine sodium (UNa) are neither accurate nor of clinical use in the ICU.<sup>71</sup> For AKI in critically ill, there could be a myriad of other causes beyond sepsis, which need to be systematically worked up for.<sup>72</sup>

### *Biomarkers in AKI*

#### *Urinary biomarkers for early diagnosis of AKI*

- We suggest measuring the urine NGAL and L-type fatty acid-binding protein (L-FABP) for early diagnosis of AKI (2B).
- We recommend against the use of urine Cystatin C for early diagnosis of AKI (UPP).

#### *Urinary biomarkers to predict AKI severity and mortality*

- We suggest measuring the urine NGAL to predict AKI severity and mortality (2C).
- We recommend against the use of the urine L-FABP and cystatin C to predict AKI severity and mortality (UPP).

### *Rationale*

In most forms of AKI, the renal tubular epithelium and not the glomeruli is the primary site of injury. Since damage first manifests in renal tubular cells, urinary biomarkers are considered more sensitive for an early diagnosis of AKI, than serum markers. Over the last two decades, several biomarkers to predict AKI early have been developed and validated including neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid-binding protein (L-FABP), kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinases-2 (TIMP-2), insulin-like growth factor-binding protein 7 (IGFBP7), and cystatin-C.

The most extensive and robust evidence to predict AKI exists for urine NGAL (uNGAL). In a 2009 meta-analysis, Haase et al. analyzed the properties of urinary, serum, or plasma concentrations of NGAL within the first 6 hours after injury or during the 24–48 hours preceding the conventional diagnosis of AKI.<sup>73</sup> The odds ratio of an elevated uNGAL in predicting the diagnosis of AKI was 18.6 (AUC of ROC curve 0.81) with a sensitivity of 76% and a specificity of 85%. The prediction accuracy was slightly better in children than in adults. NGAL also showed good correlation with the need for RRT (AUC-ROC 0.78), but not predicting the in-hospital mortality. The accuracy of plasma NGAL to predict AKI was similar to that of uNGAL. A study in a heterogeneous group of 451 critically ill adults concluded that uNGAL measured 24–48 hours before the diagnosis of AKI moderately predicted AKI in critically ill. Additionally, the median uNGAL was significantly higher among the nonsurvivors and also in the patients who required RRT.<sup>74</sup> A recent study endorsed uNGAL as a useful tool for improving AKI risk stratification.<sup>75</sup> The largest meta-analysis of 52 observational studies published in 2020, with 13,040 participants, by Albert et al. showed that uNGAL was a good predictor of the development of AKI (AUC-ROC: 0.7), severe AKI (AUC-ROC: 0.75), and dialysis-dependent AKI (AUC-ROC: 0.8).

Urine NGAL cut-off value of 589 ng/mL showed a sensitivity of 24% and specificity of 95% in predicting AKI requiring dialysis (AKI-D).<sup>76</sup>

Doi et al. measured five different urinary biomarkers (L-FABP, uNGAL, Cystatin C, IL-18, and Albumin) in 339 critically ill adult patients on admission to a medical-surgical ICU of whom 131 developed AKI. They concluded that the best urinary biomarker to detect AKI was urinary L-FABP.<sup>77</sup> A 2013 meta-analysis by Susantitaphong et al. of seven studies showed good sensitivity (74.5%) and specificity (77.6%) of L-FABP for predicting the development of AKI but performed poorly in predicting the need for dialysis.<sup>78</sup>

A 2011 systematic review/meta-analysis showed the sensitivity of 0.52 for the early diagnostic capacity of urinary cystatin C and the specificity of 0.70, with an AUC of 0.64. The evidence indicates that the urinary cystatin C is of limited utility for the early diagnosis of AKI.<sup>79</sup>

Markers of cell-cycle arrest such as tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are the more recent biomarkers of AKI. Meta-analyses have assessed the accuracy of TIMP-2 and IGFBP7 in predicting AKI.<sup>80,81</sup> Recently, the US food and drug administration (US-FDA) has approved it for clinical use, but use in the critically ill remains to be established.

The evidence is still evolving for biomarkers in predicting the need for RRT. Klein et al. in 2018 concluded from 63 studies of biomarkers in AKI, that several biomarkers promised to be reasonable predictors of RRT but the strength of evidence was not strong enough to use them routinely to guide initiation of RRT.<sup>82</sup> A 2020 ADQI consensus suggests that combining biomarkers with clinical parameters may be a superior strategy in terms of timing RRT.<sup>83</sup>

Biomarkers have been explored regarding their utility in differentiating pre-renal AKI, septic AKI, and also in postexposure prediction of AKI development. In the absence of robust evidence, we feel that these contentious issues do not warrant much contemplation at present and are best left for future consideration.

Similarly, cost-benefit analyses of their utility have not been sufficiently addressed which is an important issue in resource limited ICUs. Their overall availability and cut-off values need careful consideration by the individual ICUs while adopting them in their clinical decision-making algorithm.

### *Drug Dosing in AKI*

- We suggest a regular review of medications in ICU by a clinical pharmacist to reduce the drug related adverse events and dosing errors in AKI patients (2B).
- We recommend against the use of aminoglycosides in patients with AKI, if less nephrotoxic alternatives are available (1A).

### *Rationale*

Adjustment of drug dosing for patients with AKI is a standard clinical practice. Accurate measurement of renal function to base the drug dose and the impact of RRT on drug pharmacokinetics remains a challenge in clinical practice. The accepted methods of estimating renal function like equation-based eGFR do not generally give accurate results in AKI.<sup>84</sup> In addition, drug dosing may change with fluid status, bolus vs continuous infusion, and mode of RRT chosen.<sup>84</sup> In critically ill patients several factors might contribute to changes in the volume of distribution (Vd) and drug pharmacokinetics causing variability in drug concentrations at the site of action.

Patients with AKI often have complex medical problems and generally receive multiple drugs. This can result in adverse drug interactions, inappropriate prescribing, omissions, and under- or overdosing. Studies have shown that the inclusion of pharmacist in ICU multidisciplinary team can reduce rates of adverse drug events, dosage errors including renal dose adjustment, drug interactions, and drug incompatibilities.<sup>85,86</sup>

Appropriate antimicrobial selection based on local epidemiology and resistance, dosing and infusion strategies, mode of RRT, co-morbidities, residual renal function, and patient's response are only some of the variables that must be considered while prescribing antimicrobials for critically ill patients with AKI, to optimize clinical outcomes.

Aminoglycosides are generally highly efficacious antimicrobials but their use is limited by a side effect profile that includes up to a 25% increased risk of causing or worsening AKI.<sup>87</sup> They should not be used for empirical or first-line treatment in AKI unless no suitable alternatives are available. If the administration of aminoglycosides is essential, their use should be restricted for as short a duration as possible and in a single daily dose, to avoid nephrotoxicity.<sup>87</sup> Aminoglycoside levels can vary across individuals which necessitates the use of therapeutic drug level monitoring.<sup>88</sup> KDIGO guidelines 2011 recommend drug level monitoring for aminoglycosides if used as multiple daily doses for 24 hours and single daily dose for 48 hours.<sup>84</sup>

There is an increased risk of nephrotoxicity with concurrent therapy of vancomycin and an aminoglycoside.<sup>89</sup> Vancomycin nephrotoxicity as monotherapy is also a concern but there is insufficient literature available to make any recommendation. A recent study reported a significantly lower than anticipated nephrotoxicity with vancomycin. Its use was associated with severe AKI only when serum drug trough level was more than 20 mg/L but no association was seen with the need for RRT.<sup>90</sup> There may be a role for therapeutic drug dose monitoring for antimicrobials wherever available.

Renal toxicity with Amphotericin B is well established. KDIGO guidelines have previously suggested using lipid rather than conventional formulations of Amphotericin B to minimize nephrotoxicity.<sup>84</sup> However, even Liposomal Amphotericin B can cause nephrotoxicity.<sup>91</sup> There is evidence that other antifungal agents—azoles and echinocandins—may have therapeutic efficacy similar to Amphotericin B while being intrinsically less nephrotoxic.<sup>92</sup>

### Nutrition in AKI

- We recommend that ICU patients with AKI should receive energy upto 25–30 kcal/kg/day, equivalent to 100–130% of resting energy expenditure (1A).
- We suggest the following protein intake in AKI with critical illness:
  - Not on RRT: 1.3 g/kg/day up to 1.7 g/kg/day (2B).
  - On intermittent RRT: 1 g/kg/day up to 1.5 g/kg/day (2B).
  - On CRRT: up to 1.7 g/kg/day (2B).
- We recommend not to restrict the protein intake with renal insufficiency to avoid or delay initiating RRT (UPP).

### Rationale

The nutritional requirements in the patients with AKI should be individualized based on the pre-existing nutritional status, catabolic rate, severity of AKI, underlying disease causing AKI, comorbidities,

and the type and intensity of RRT. The research on nutrition in AKI suffers from a paucity of high-quality studies; the majority of studies being of small sample size, nonrandomized study design, and lacking stratification for the severity of illness.

Since AKI in ICU is almost always a part of multi-organ dysfunction, the energy requirements are that of a critically ill patient, in whom measured energy requirements should be equivalent to 100–130% of resting energy expenditure to maintain a positive nitrogen balance.<sup>93</sup> KDIGO recommends a calorie intake of 25–30 kcal/kg/day for critically ill patients with AKI, whereas the society of critical care medicine (SCCM) suggests 25–35 kcal/kg/day.<sup>8,94</sup> Ficcadori et al. compared a calorie intake of 40 vs 30 kcal/kg/day and concluded that higher calorie intake did not improve the nitrogen balance but was associated with increased risk of artificial nutrition-related side-effects such as hyperglycemia, hypertriglyceridemia, and higher positive fluid balance.<sup>95</sup> In contrast, a large prospective observational study of 595 patients with AKI showed that low caloric and protein intake, negative nitrogen balance, and low albumin value were associated with higher hospital mortality.<sup>96</sup> Thus, energy requirements should be individualized based on several factors including catabolic rate and renal function. Energy contribution from solutions such as lactates, citrate should be counted in those receiving CRRT.

Protein requirements in AKI patients vary widely and an optimal protein requirement is still debated. A positive nitrogen balance is found to be associated with significantly better ICU and hospital survival. An RCT by Scheinkestel et al. reported that an increase in nitrogen balance by 1 g/day improved survival by 21% in the CRRT group.<sup>97</sup> The protein requirement should also be individualized and prescribed according to the catabolic rate, renal function, protein, and amino acid losses during RRT. The AKI patients not on RRT would require protein supplements of 1.3–1.7 g/kg/day.<sup>8,98,99</sup> In those receiving IHD, protein intake should be 1–1.5 g/kg/day.<sup>8,94</sup> and the patients receiving CRRT should receive a higher protein intake, up to a maximum of 1.7 g/kg/day.<sup>8,99</sup> Ficcadori et al. recommend a protein intake of a maximum of 2 g/kg/day in AKI patients with or without CRRT.<sup>100</sup> However, it is difficult to achieve such a high protein intake in clinical practice, considering the fluid restrictions imposed on these patients and associated cardiac abnormalities.

RRT especially CRRT is associated with a large amount of amino acid losses, up to 10–15 g/day in the effluent. Cochrane Renal Group in 2010 reviewed 8 RCTs including 257 participants and concluded that the use of essential amino acids (EAA) shortened the overall duration of kidney dysfunction and improved survival in dialysis-dependent AKI compared to those who received hypertonic glucose but found no significant difference in mortality between EAA and general amino acids.<sup>101</sup>

Urea nitrogen appearance is lower in patients with a lower protein intake and hence may facilitate postponing the need for dialysis.<sup>101</sup> However, such a strategy may result in a significant negative nitrogen balance which is associated with increased mortality.<sup>96</sup> Hence, the practice of restricting protein intake in AKI patients to prevent or postpone dialysis should be discouraged.

Micronutrient deficiency is common in critically ill with severe AKI patients irrespective of whether receiving CRRT or not.<sup>102</sup> However, the relative contribution of the loss of micronutrients in dialysis to the overall deficiency and the outcome of patients is unclear. Overzealous supplements of micronutrients such as vitamin C may have a deleterious effect since vitamin C promotes calcium oxalate crystal deposition in the kidney thereby worsening AKI.<sup>103</sup>

Early high-dose vitamin D supplementation also did not show a survival advantage at 90 days in a randomized study.<sup>104</sup>

#### AKI Recovery and Follow-up

- We recommend that all patients who survive an episode of AKI of any stage should be assessed at the end of 1 month of onset of AKI with AKI follow-up bundle and reviewed by a primary care physician or nephrologist (1B).
- We suggest that for long-term monitoring, the AKI follow-up bundle be performed by a physician or a nephrologist once a year for category-1, and once in 6 months for category-2 patients (2C).
- We recommend that category-3 patients who carry a high risk of progression to CKD and end-stage renal disease (ESRD) should be followed up by a nephrologist, from the time of hospital discharge, at an interval deemed necessary by the nephrologist (1B).

#### Rationale

The patients who survive an episode of AKI in ICU carry an increased risk of mortality, cardiovascular events (acute coronary syndromes, HT, stroke), progression of pre-existing CKD, and new-onset CKD.<sup>105</sup> The factors which increase the risk of poor outcome are pre-existing CKD, stage III AKI especially those who needed RRT during the ICU stay, older age, presence of co-morbidities especially DM, HT, cardiovascular diseases, malignancy, and CLD.<sup>106</sup> The goal of post-AKI monitoring is to mitigate the progression of AKI and improve short-term and long-term complications by timely and effective care protocols.

AKI requiring dialysis (AKI-D) occurs in 1–2% of hospitalized patients, increasing annually by 10% and is associated with increased risk of both in-hospital and postdischarge mortality.<sup>106</sup> Approximately 10–30% of patients with AKI-D who survive hospital discharge will require outpatient dialysis.<sup>106</sup> Furthermore, 1 out of 12 AKI-D patients who become dialysis independent at hospital discharge would reach end-stage renal disease and resume dialysis within 3–5 years.<sup>107</sup> There have been many models predicting risk factors associated with outcomes with conflicting results.<sup>108</sup>

The patients who develop AKI can be stratified into three categories as shown in Table 4. The patients having AKI in ICU should be followed up with AKI follow-up bundle (Table 5) as per the AKI category they fall in.

**Table 4:** Categories of acute kidney injury (AKI) patients

| Category 1                | Category 2                                | Category 3   |
|---------------------------|---|--|
| AKI Stage-1 <1 week       | AKI Stage-1 >1 week or Stage-2            | AKI Stage-3; Recurrent AKI; AKI-D                        |
| No/limited comorbidities* | Increasing comorbidities*                 | Advanced age >65 years, Cardiovascular disease, Diabetes |
| No underlying CKD         | Pre-existing CKD-1-3 (eGFR >30 mL/minute) | Pre-existing CKD-4 (eGFR <30 mL/minute)                  |

\*Comorbidities include diabetes mellitus, hypertension, cardiovascular disease, malignancy, chronic liver disease; AKI, acute kidney injury; AKI-D, acute kidney injury on dialysis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

**Table 5:** Acute kidney injury (AKI) follow-up bundle

| AKI follow-up bundle includes                                       |
|---|
| Blood pressure measurement  |
| Serum creatinine  |
| e-GFR   |
| Urine dipstick for proteinuria and quantification when positive     |
| Checking medications (for nephrotoxicity and dose adjustments)      |
| Appropriate use of RAAS blockade for underlying proteinuria and CKD |

AKI, acute kidney injury; e-GFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; CKD, chronic kidney disease

## RENAL REPLACEMENT THERAPY

### Introduction

RRT use in AKI in ICUs varies from 5 to 40%. Currently there is no consensus on the timing of initiation, mode, optimal dose, and discontinuation of RRT or its use for nonrenal indications. Similar is the case about type of dialysis hardware and choice of anticoagulation. The ISCCM AKI guidelines committee formed a consensus on 12 major issues concerning RRT for AKI in critically ill patients.

#### Indications of RRT in AKI

- We recommend RRT for life-threatening conditions such as severe hyperkalemia, severe metabolic acidosis, and fluid overload that are resistant to medical therapy causing severe cardiopulmonary compromise and other uremic complications that are unresponsive to medical therapy (1C).
- We recommend against prophylactic use of RRT to prevent uremic complications (UPP).
- We recommend against prophylactic RRT for removal of contrast agent in patients with increased risk of CIN (1A).

#### Rationale

RRT is used as a mode of treatment for several “renal” and “nonrenal” conditions in acute care settings.

The absolute and relative indications for initiating RRT in patients with AKI are shown in Table 6. There are no RCTs, systematic reviews, or meta-analyses available for the absolute or conventional indications for initiation of RRT. However, clinical judgment and medical ethics dictate that when an effective treatment to correct a life-threatening condition is available, it should be used even in the absence of formal evidence. There is categorical agreement on this by experts and international guideline bodies.<sup>8</sup> By contrast, in the absence of absolute indications, some experts propose that initiation of RRT be considered when the metabolic and fluids demands exceed the kidney's capacity to meet them.<sup>109</sup> However, specific parameters to qualify and quantify the metabolic derangements and renal capacity have not been assessed in clinical studies, and there are no studies to show that such a strategy improves outcomes in AKI.

CIN is one of the common causes of iatrogenic AKI. Though RRT done soon after the administration of IV contrast agent is effective in removing the contrast agent, it may not entirely prevent CIN.

Cruz et al.,<sup>110</sup> in their 2012 meta-analysis (nine RCTs and two nonrandomized trials,  $n = 1010$ ) concluded that periprocedural RRT did not decrease the incidence of radiocontrast-induced nephropathy (RCIN); the need for permanent RRT or progression to end-stage renal disease, compared to standard medical therapy. In another study 6 years later, Pistolesi et al. also did not find HD or hemofiltration to be protective against CIN.<sup>111</sup>

RRT is also used for “nonrenal” conditions like removal of cytokines in sepsis, removal of dialyzable poisons and toxins, control of body temperature, and severe resistant-to-treatment electrolyte disturbances such as hypercalcemia, hyponatremia, hypermagnesemia, etc. The decision of initiation of RRT in most of these conditions is highly individual and should depend on associated symptoms rather than absolute values.

**Table 6:** Indications for initiating RRT in patients with AKI

|                      |   |
|----------------------|---|
| Absolute indications | Refractory hyperkalemia ( $K > 6.5$ mEq/L).   |
|                      | Refractory acidemia (metabolic or mixed acidosis with $pH < 7.15$ ).                              |
| Relative indications | Signs and symptoms of uremia (bleeding diathesis, pericarditis, encephalopathy).                  |
|                      | Refractory volume overload with organ edema.  |
|                      | Toxicity or overdose of easily dialyzable medications or drugs.                                   |
|                      | Progressive Oliguria/anuria ( $UO < 200$ mL/24 hours) unresponsive to medical management.         |
|                      | Progressive Azotemia; $BUN > 100$ mg/dL unresponsive to medical management.                       |
|                      | Life-threatening electrolyte derangements (hypermagnesemia, hypercalcemia) in the setting of AKI. |
|                      | Hyperthermia refractory to regular cooling techniques.  |
|                      | Anticipating worsening electrolyte problems with AKI (tumor lysis syndrome, rhabdomyolysis).      |

AKI, acute kidney injury; K, potassium level; UO, urine output; BUN, blood urea nitrogen

### Timing of Initiation of RRT in AKI

- We recommend that RRT be initiated urgently in patients who meet one or more of the absolute indications (1A).
- For nonurgent indications we suggest that RRT may be considered when the capacity of the kidneys cannot meet the metabolic demands imposed by AKI on the body (UPP).

### Rationale

There is wide variation in clinical practice about timing of RRT in critically ill patients. The theoretical advantages and disadvantages of early initiation of RRT are summarized in Table 7.

Published studies on this topic suffer from lack of uniformity in the study design, patient population selection, definition of early and late initiation, and modality of RRT. In the ELAIN trial,<sup>112</sup> delayed initiation was defined as RRT initiation within 12 hours of the diagnosis of KDIGO stage III AKI, but based on this criteria, some of these patients would have been labeled as early RRT in the subsequent IDEAL-ICU,<sup>113</sup> AKIKI,<sup>114</sup> and STARRT AKI<sup>115</sup> trials.

The beneficial effects of early initiation of RRT reported in observational studies have not been supported by larger randomized clinical trials. Three of the four large RCTs in the last decade, the IDEAL-ICU, AKIKI, and STARRT-AKI,<sup>113–115</sup> did not show mortality benefit with early initiation of RRT. ELAIN,<sup>112</sup> the lone study to show any such benefit, suffers from being a single center study, with mostly surgical patients with low fragility index and its results were potentially skewed as many early initiation RRT patients might have recovered without a need for RRT. It is unsurprising that most meta-analyses did not find any difference in mortality, duration of hospital stay, and renal recovery between early and late initiation of RRT.<sup>116,117</sup>

Acute Dialysis Quality Initiative (ADQI) consensus group<sup>118</sup> has proposed a demand and capacity model in AKI and suggests initiating RRT when fluid and metabolic demands exceed kidney capacity.

For the above reasons, we recommend not to initiate early RRT unless for absolute life-threatening indications or medical refractory complications.

**Table 7:** Rationale for early initiation of renal replacement therapy (RRT)

| Advantages  | Disadvantages   |
|---|---|
| Prevention of severe electrolyte and acid-base imbalances   | Complications associated with vascular access placement.  |
| Better volume management  | Catheter-related bloodstream infections.  |
| Prevention of uremic complications  | Complications due to anticoagulation for RRT.   |
| Recovery of distant organ injury and prevention of early AKI induced impact to vital organs such as heart, liver, lungs, brain, and liver resulting from electrolyte–metabolic imbalance, fluid overload, and systemic inflammation | Bio-incompatibility reactions to dialyzer membranes.  |
|   | Rapid changes in electrolyte concentrations.  |
|   | Clearance of vital medications with particular concern of underdosing of antibiotics.             |
|   | Nutrient depletion.   |
|   | Hemodynamic changes and maladaptive neuro-hormonal after RRT resulting in delayed renal recovery. |
|   | Increased health-care cost.   |
|   | Spontaneous renal recovery in some patients—unnecessary RRT exposure.                             |

AKI, acute kidney injury; RRT, renal replacement therapy

### Modality of RRT in AKI

- We suggest that the choice of RRT modality be based on the availability of facility, experience, and expertise of medical staff and the clinical status of the patient (UPP).
- We recommend the use of continuous renal replacement therapy (CRRT) or sustained low efficiency dialysis (SLED) rather than intermittent hemodialysis (IHD) in patients who are hemodynamically unstable and may have intolerance to fluid removal (1B).
- We recommend IHD for rapid correction of life-threatening hyperkalemia with cardiac arrhythmias (1B).
- We suggest the use of IHD or SLED over CRRT and peritoneal dialysis (PD) for rapid correction of metabolic acidosis (2C).
- We recommend CRRT over IHD or SLED in patients with acute brain injury or increased intracranial tension (1B).
- We suggest the use of CRRT, SLED, or IHD over PD for hypercatabolic patients (2C).

### Rationale

With advances in technology over the last several decades, we have a broad choice about modalities of RRT for critically ill patients with AKI that can be classified into continuous and intermittent therapies (Table 8).

Several factors influence the decision to choose a mode of RRT in ICU (Table 9).<sup>8,119</sup> In developing countries, clinicians face

**Table 8:** Modalities of RRT available for AKI in critically ill patients

| <i>Continuous therapies</i>   |
|---|
| • Continuous renal replacement therapy (CRRT) <ul style="list-style-type: none"> <li>– Continuous venovenous hemofiltration (CVVH)</li> <li>– Continuous venovenous hemodialysis (CVVHD)</li> <li>– Continuous venovenous hemodiafiltration (CVVHDF)</li> </ul> |
| • Peritoneal dialysis (PD)  |
| <i>Intermittent therapies</i>   |
| • Intermittent hemodialysis (IHD)   |
| • Hybrid therapies <ul style="list-style-type: none"> <li>– Sustained low efficiency hemodialysis (SLED)</li> <li>– Sustained low efficiency hemodiafiltration (SLED-f)</li> </ul>  |

additional challenges like resource scarcity, lack of expertise, and financial constraints.<sup>119</sup>

Most RCTs and systematic reviews comparing CRRT and intermittent therapies such as IHD and SLED have failed to show any survival benefit or significant difference in recovery of renal function with either modality of RRT in ICU.<sup>120–124</sup> SLED is less labor-intensive and less expensive compared to CRRT and hence can be a suitable alternative in resource and expertise-limited settings. A 2007 meta-analysis showed significant improvement in hemodynamic parameters in patients receiving CRRT compared to IHD<sup>124</sup> whereas hemodynamic stability was similar between CRRT and SLED in another meta-analysis<sup>122</sup> indicating that CRRT and SLED are preferable to IHD in hemodynamically unstable patients with AKI.

PD in ICU has not been discussed in detail in the guidelines for the lack of evidence in the literature. The comparative studies of PD are very limited in adult patients with AKI. In comparative studies neither PD nor high-volume PD (HVPD) showed any advantage over daily HD or hemofiltration.<sup>125,126</sup> An RCT of 125 patients with AKI reported significantly better 28-day survival, renal recovery rates, and reduced infectious complications in the tidal PD (TPD) group compared to the CVVHDF group.<sup>127</sup> These small studies indicate that modifications in PD to improve efficacy such as TPD and HVPD may be considered as viable alternative RRT in resource-limited conditions.

Experience of hemodialysis in end-stage renal disease patients shows that IHD is effective in rapidly reducing serum potassium levels in patients with severe hyperkalemia.<sup>128</sup> IHD is thus preferred in patients with life-threatening hyperkalemia, with a massive and rapid release of potassium due to cell lysis such as rhabdomyolysis and tumor lysis syndrome. In patients with nonlife-threatening hyperkalemia with hemodynamic instability, CRRT or SLED may be used.<sup>128</sup>

A rapid correction of metabolic acidosis may be achieved with IHD and SLED. However, the choice of RRT modality should be guided by the rate of acid generation, the cause and type of acidosis, and the hemodynamic status of the patient. The observational studies have shown that severe lactic acidosis with hemodynamic instability can be effectively managed by CRRT using bicarbonate-based solutions.<sup>129</sup> On the other hand, IHD resulted in a faster correction of acidosis and removal of toxic metabolites in methanol

**Table 9:** Factors influencing the choice of initial mode of RRT in AKI in ICU

| <i>Patient-related factors</i>  | <i>Resource and personnel-related factors</i>                         |
|---|---|
| • Severity of critical illness and its trend                                | • Availability of the RRT modality                                    |
| • Organ dysfunction other than kidney                                       | • Clinical expertise of the provider of RRT                           |
| • Presence of life-threatening complication of uremia                       | • Available resources to provide RRT                                  |
| • Hemodynamic status  | • Availability of technical support to provide uninterrupted RRT      |
| • Comorbidities   | • Type of hospital setting (rural, urban, public, private, corporate) |
| • Hypercatabolic state  | • Personal preferences of intensivist/nephrologist                    |
| • Increased intracranial tension  | • Cost of therapy   |
| • Expected benefit from therapy in terms of survival and long-term outcomes |   |
| • Need for fluid removal  |   |
| • Need to mobilize the patient  |   |
| • Potential complications specific to a mode of RRT                         |   |
| • Expected long-term outcome and quality of patient                         |   |

RRT, renal replacement therapy

poisoning and no statistical difference was seen in survival between IHD and CRRT treatment groups.<sup>130</sup>

IHD may lead to hemodynamic instability, rapid osmolar shifts in brain, increase in intracranial pressure due to increased brain water content and reduced blood flow velocity in the brain which can adversely affect patients with acute brain injury and increased intracranial pressure,<sup>131</sup> thereby making CRRT the preferred modality in these clinical settings. PD may also be beneficial in such settings, but relevant clinical studies are missing.

Hypercatabolic status is common in critically ill patients especially in patients with sepsis and burns which leads to excessive breakdown of proteins causing increased generation of urea and other nitrogenous waste products with a consequent high metabolic demand on RRT. The clearance of these uremic toxins is best achieved with CRRT, IHD, and SLED than with PD. A few studies reported good metabolic control with HVPD and TPD but did not report catabolic rate in their patient populations.<sup>126,127,132</sup> Moreover, PD is associated with a large amount of protein loss in the effluent. For these reasons, PD appears to be an inferior modality in hypercatabolic AKI patients compared to CRRT, IHD, and SLED.

### RRT Hardware

#### Catheters

- We suggest using nontunneled dialysis catheter in critically ill patients for short duration RRT (2B).
- We recommend the use of double lumen catheters over triple lumen or single lumen catheters (UPP).
- We recommend the use of ultrasonography (USG) guidance for insertion of vascular access and by trained personnel when available (1A).
- We recommend that the position of dialysis catheter inserted in the internal jugular and subclavian veins be confirmed radiologically (1A).
- We recommend internal jugular vein (IJV), preferably right IJV as the first choice for vascular access followed by the femoral veins. The subclavian veins are the least preferred sites for dialysis catheter (1A).
- We recommend against antibiotic prophylaxis prior to catheter insertion (1A).
- We recommend against regular timed change of dialysis catheters unless it is blocked or shows signs of infection (1B).

#### Dialysate Membranes

- We recommend the use of biocompatible membranes for hemodialysis in a patient with AKI (1A).

### Rationale

#### Hemodialysis Catheters

- **Choice of catheter:** To allow a high blood flow rate through a HD catheter, the surface-to-volume ratio should be as high as possible, and an angular conformation of the lumen should be avoided. A catheter size between 12 and 16 French is sufficient for all RRT modalities used in ICU.

The lone small, randomized trial that compared the use of tunneled and non-tunneled catheters in AKI via femoral access<sup>133</sup> found that use of a tunneled catheter required a longer time to insert but had a lower incidence of vein thrombosis and catheter-related infection and a better ratio of venous return pressure to catheter blood flow and dialysis efficiency. There are certain

contraindications to insertion of a tunneled catheter in a critically ill patient—emergent need, hemodynamic instability, coagulopathy and positive blood cultures. Also, the ease of insertion and the shorter duration of need for RRT makes the nontunneled catheters preferred ones.

The triple lumen dialysis catheters compromise the size of the dialysis lumens and there is a risk of medications administered through the third lumen during dialysis getting quickly dialyzed.

There is a paucity of evidence evaluating the advantage of using surface-coated nontunneled HD catheters in the ICU.

- **Insertion:** The use of real-time USG guidance for HD catheter insertion was found to significantly reduce the failure of catheter placement on the first attempt, risk of arterial puncture and subsequent hematomas when compared to the landmark method. Also, the time taken for successful cannulation was significantly lower and there were fewer attempts needed for catheter insertion.<sup>134</sup>

Chest radiography should be done after the placement of catheters in the IJV and subclavian veins before the initiation of the RRT session. This helps to verify the position of the catheter tip in the superior vena cava and pick up any iatrogenic pneumothorax.

The preferential site for HD catheter insertion is the straighter right IJV. The left IJV access can induce turbulence due to its anatomical curve, causing chances of catheter dysfunction and postcatheterization venous stenosis.<sup>135</sup> Up to 40% of subclavian venous accesses may induce venous stenosis. Use of jugular access does not reduce the risk of infection as compared to femoral access except in patients with a BMI >28 kg/m<sup>2</sup>.<sup>136</sup> Hence, the internal jugular vein may be the preferred dialysis catheter access in obese patients. No antibiotic prophylaxis is needed before the insertion of nontunneled hemodialysis catheters.<sup>137,138</sup>

- **Maintenance:** There is no advantage offered by a regular timed change of dialysis catheters.<sup>138</sup> The change should be clinically directed by catheter dysfunction, infection at the insertion site, and suspicion as the source of central line-associated blood stream infection.

#### Dialysate Membranes

A meta-analysis including 722 patients found that biocompatible cellulose acetate membranes were more beneficial than synthetic biocompatible membranes over bio-incompatible cuprophane membranes.<sup>139</sup> Another meta-analysis of 10 prospective trials and 867 patients found survival advantage with the use of biocompatible synthetic membranes over biocompatible cellulose-based membranes; however, this advantage was not seen in chances of renal recovery.<sup>140</sup>

#### Monitoring during RRT

- We recommend a protocol-based template for prescribing and monitoring RRT and detailed documentation of the treatment (UPP).
- We recommend monitoring patient-related factors and biochemical parameters tailored as per the individual need of the patient (UPP).
- We suggest monitoring the delivered dose of RRT (2C).

### Rationale

*National Confidential Enquiry into Patient Outcome and Death (NCEPOD)* in the United Kingdom in a review of the care received by the patients who died of AKI concluded that the care received in AKI and patients receiving RRT for AKI was suboptimal.<sup>141</sup> It is generally

believed that the standardized protocols for RRT tailored to the local needs based on patient case mix, economics, and resource issues, would help to improve the quality, efficacy and safety of RRT. However, this has not been systematically studied.

The monitoring of RRT is an essential part of the treatment to ensure safe delivery of the therapy. It helps to ensure that the prescribed treatment is delivered, to modify the treatment responses to the changing demands of the patients (dynamic prescription), to prevent complications related to RRT, and to identify the degree of compliance with the “quality monitors” set for RRT by the individual programs.

Table 10 shows a wide range of parameters that can be monitored during RRT to ensure the effective and safe delivery of RRT. The individual ICUs could pick and choose from these components and the frequency of performing the tests to structure their monitoring protocols which are relevant to local needs. However, hemodynamic parameters, biochemical concentrations, fluid balance, and acid-base status form the essential components for monitoring RRT.

Close monitoring of blood pressure during RRT is of paramount importance since it is associated with significant morbidity and delayed renal recovery.<sup>142</sup> Electrolyte disturbances are commonly observed in CRRT including hypokalemia and hypophosphatemia. Hypocalcemia as well as hypercalcemia are more common in regional citrate anticoagulation (RCA). Monitoring fluid status and managing fluid balance also constitute an important component of monitoring during RRT since fluid accumulation of >10% of body weight in critically ill patients with AKI is shown to be associated with increased morbidity and mortality.<sup>142</sup>

The dose of the RRT delivered needs monitoring since it can be lower by up to 20–30% than the prescribed dose.<sup>143</sup> Claire-de Granado et al. evaluated six methods of blood-side and dialysate-side kinetics to measure the solute clearance and recommended dialysate-side measurements (expressed as mL/minute) for CRRT and blood-side measurements for intermittent RRT (expressed as Kt/V urea).<sup>144</sup>

The ICUs who provide RRT regularly are encouraged to develop their protocols to initiate, prescribe, deliver, monitor, and terminate RRT. It is also desirable to adapt “quality indicators” to monitor the performance of the RRT program and modify protocols after going through the feedback generated through the review process.<sup>145</sup> Some of the quality indicators suggested for CRRT are (1) downtime duration, (2) life-span of the filter, (3) incidence of bleeding complications while receiving anticoagulation (4) percentage of prescribed dose delivered and (5) incidence of dialysis catheter-related infections.<sup>146</sup>

#### Dose of CRRT in AKI

- We recommend an individualized and prescribed dose of RRT, signed by an Intensivist or Nephrologist before the start of each session (UPP).
- We recommend that RRT prescription be assessed and revised from time to time till the optimal goal of therapy is achieved (UPP).
- We recommend a delivered dose of CRRT of 20–25 mL/kg/hour of effluent volume (1A).
- We recommend against the use of high intensity or intensive dose of CRRT (1A).
- We suggest that pre-dilution factor be taken into consideration while prescribing CRRT to prevent under delivery of the dose (UPP).

#### Rationale

Despite all research and advances, prescribing the correct dose for RRT in AKI has been challenging in clinical practice.

The urea kinetic model (kt/v) for dose quantification of RRT is validated in patients with CKD but its usage in AKI remains questionable. Patients suffering from AKI have altered volume of distribution, metabolic instability, negative nitrogen balance, and hemodynamic instability with altered regional perfusion and disequilibrium of urea distribution. Despite this heterogeneity, Pagnini et al. demonstrated a survival benefit with a urea reduction rate (URR) >58% (kt/v >1) in their retrospective analysis of patients with AKI of intermediate severity.<sup>147</sup>

In a single-center study on 160 AKI patients by Stiffel et al. randomized to receive IHD daily or on alternate days,<sup>148</sup> the 14-day mortality was lower in the daily IHD group compared to the alternate-day IHD group (28 vs 46%,  $p = 0.01$ ) and a closer analysis indicated that the survival benefit in the daily IHD group was possibly due to under-dose of dialysis in the alternate-day IHD group.

The dose of CRRT is quantified by *the effluent volume per unit time normalized to the body weight of the patient* (unit: mL/kg/hour). Ronco et al., in 2002, compared three doses of effluent volumes (20, 35, and 45 mL/kg/hour) in a single-center study of 425 patients undergoing post filter CVVH. The survival rates in these three groups were 41, 57, and 58%, respectively, after 15 days of discontinuation of CRRT.<sup>149</sup>

The VA/NIH ATN trial across 27 medical centers in North America included 1,124 critically ill patients with AKI randomized to either intensive (40 mL/kg/hour) or less intensive (25 mL/kg/hour) IHD/SLED/CVVHDF group.<sup>150</sup> There was no significant difference in death from any cause by day 60 (53.6 vs 51.5%,  $p = 0.047$ ), in-hospital death or recovery of kidney function by day 28. Hypotension requiring vasopressor support, hypokalemia, and hypophosphatemia were significantly more in the intensive group.

The Randomized Evaluation of Normal vs Augmented Level (RENAL) trial in 35 ICUs across Australia and New Zealand included 1,508 critically ill patients with AKI assigned to either higher (40 mL/kg/hour) or lower intensity (25 mL/kg/hour) CRRT in CVVHDF mode.<sup>151</sup> No differences were noted in all-cause death at 90 days, ICU death, in-hospital death after ICU discharge, ICU duration, duration of mechanical ventilation, duration of RRT, dialysis status at day 90 or new organ failures between the two groups. The post-hoc analysis of the ATN trial showed that the low-intensity group had higher RRT free days through day 28 compared to the high-intensity group (mean difference 2.5 days, 95% CI: –4.79 to –2.7 days,  $p = 0.028$ ) indicating that more frequent intermittent dialysis was associated with delayed renal recovery in AKI.<sup>152</sup> Hypophosphatemia was more common in the higher-intensity group but there was no difference in the incidence of other adverse events such as arrhythmias, disequilibrium, and hypokalemia.

Several meta-analyses have evaluated the effect of CRRT dose in AKI. Van Wert et al.<sup>153</sup> assessed 12 studies with 3,999 patients and showed no benefit of more intensive RRT regarding survival or dialysis dependence among survivors. Li et al.<sup>154</sup> assessed eight studies with 2,970 patients and concluded that high-dose and low-dose hemofiltration have similar outcomes for mortality, ICU length of stay, and hospital stay in critically ill patients with AKI.

The futility of high-volume hemofiltration became clear post IVOIRE trial in 2013, which compared 35 vs 70 mL/kg/hour (combined pre/post-dilution) hemofiltration and showed no

**Table 10:** Monitoring during RRT

| <i>Principles</i>  |   |   |
|--|---|---|
| <ul style="list-style-type: none"> <li>• To ensure that the prescribed therapy is delivered during RRT</li> <li>• To modify the treatment protocols to meet the changing demands</li> <li>• To prevent complications related to RRT</li> </ul> |   |   |
| <i>Clinical, hematological, biochemical, and imaging parameters to be monitored</i>  |   |   |
| <b>Neurological status</b>   |   |   |
| Look for dialysis disequilibrium syndrome  | Patients who had CKD and currently initiated on renal replacement therapy               |   |
| GCS  | Daily   |   |
| <b>Hemodynamic parameters</b>  |   |   |
| Clinical parameters  | Edema, daily weight, JVP, heart and lung auscultation                                   | Need hourly monitoring depending on clinical status   |
| Static/dynamic parameters  | CVP, PCWP/SVV, PPV, Aortic flow velocity  | As per availability and based on clinical status  |
| <b>Fluid status</b>  |   |   |
| Cumulative balance   | Daily   |   |
| Continuous intake and output chart   | Hourly for those on CRRT  |   |
| <b>Acid-base status</b>  |   |   |
| Blood gas analysis   | Every 6th hourly at initial presentation  | Once-daily after hemodynamic stabilization  |
| <b>Electrolytes</b>  |   |   |
| Potassium  | 8th hourly initially  | Once-daily after achieving stable levels  |
| Sodium, magnesium, phosphorus, calcium   | Daily, SNa monitored at least 6-hourly while on CRRT                                    |   |
| <b>Anticoagulation</b>   |   |   |
| Unfractionated heparin   | APTT, Activated clotting time   | 4th hourly  |
| Regional citrate anticoagulation   | Blood gas analysis and ionized calcium  | 4th hourly initially and 8th hourly after achieving stable acid-base status and ionized calcium level |
| Citrate accumulation index = Ratio of total calcium to ionized calcium   | Daily   |   |
| <b>Blood parameters</b>  |   |   |
| Hemoglobin, WBC count, platelet count  | Daily   |   |
| <b>Solute clearance</b>  |   |   |
| Blood urea, serum creatinine urea  | Daily   |   |
| Kt/V, URR; prescribed dose in CRRT; Delivered dose   | Daily   |   |
| Sieving coefficient  | Effluent urea/blood urea  | Daily   |
| Clearance  | Sieving coefficient × effluent dose   | Daily   |
| Drug dosing  | Daily   |   |
| <b>Nutrition</b>   |   |   |
| Total energy intake; Protein intake  | Daily   |   |
| <b>Liver parameters</b>  |   |   |
| Serum albumin; liver enzymes; serum ammonia; serum bilirubin levels  | To be verified on initiation of RRT and for every 72 hours after clinical stabilization |   |
| <b>Vascular access</b>   |   |   |
| Exit site; blood flow through access; tunnel infection   | Daily   |   |

RRT, renal replacement therapy; CKD, chronic kidney disease; GCS, glasgow coma scale; JVP, jugular venous pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVV, stroke volume variation; PPV, pulse pressure variation; CRRT, continuous renal replacement therapy; SNa, serum sodium; APTT, activate partial thromboplastin time; WBC, white blood count; URR, urea reduction ratio

mortality difference between the two groups.<sup>155</sup> This confirmed that increasing CRRT dose/intensity above 20–25 mL/kg/hour did not improve survival in critically ill patients with severe AKI.

A meta-analysis by Junhai et al. compared 21 studies including 3,135 critically ill patients showed that mortality in patients undergoing high volume hemofiltration (HVHF) was lower ( $p = 0.004$ ) in those with sepsis and ARDS compared to the control group.<sup>156</sup> More high-quality RCTs are needed to clarify the clinical effects of HVHF in the treatment of critically ill septic patients.

Interruptions during CRRT are common due to changes in replacement solutions, circuit clotting, radiological investigations, surgical procedures, machine alarms, etc. Two additional factors must be considered while deciding the adequacy of the dose of continuous therapies. First, the downtime or the stoppage time and second the pre- or postfilter fluid replacement. The fact that machine downtime contributes to ineffective dose delivery was demonstrated by the DO-RE-MI study group.<sup>157</sup> This study also considered the effect of percentage pre-dilution in calculating the delivered dose and hypothesized that lack of attention to this aspect while prescribing the CRRT may lead to the delivery of dose lower than the prescribed dose. This necessitates an assessment of RRT treatment at regular intervals to allow for necessary adjustments to deliver the prescribed dose.

### Fluids for CRRT

#### Recommendations

- We recommend bicarbonate-based fluids over the lactate-based fluids for dialysis and replacement in CRRT (1B).
- We suggest not to use custom-made fluids for replacement in CRRT (UPP).

#### Rationale

There is no significant difference in the composition of dialysis and replacement fluids specifically designed for CRRT except for those used for citrate anticoagulation. The choice of fluids for CRRT would depend on (1) acid-base balance, (2) electrolyte and divalent ion balance, and (3) hepatic and cardiovascular performance and other organ function.<sup>158</sup>

- **Choice of buffer:** The acid-base balance is influenced by the type of buffer used in dialysis fluid (DF) and replacement fluid (RF). When RF is infused along with fluid-ultrafiltration, the losses of bicarbonate need to be balanced by an equal or higher amount in the infusion solution. In the case of metabolic acidosis, a positive buffer balance is necessary and hence a solution with a bicarbonate concentration higher than that of plasma is needed. Bicarbonate, lactate, and acetate have all been used as buffers in CRRT solutions whereas citrate has been used both as a buffer and an anticoagulant. Acetate-based fluids should be avoided in CRRT due to their deleterious effect on hemodynamics.<sup>159</sup>

Bicarbonate and lactate-based solutions have shown similar efficacy in correcting metabolic acidosis. However, patients with circulatory shock and liver dysfunction may lack the capacity to metabolize lactate to citrate in the liver and muscle. Bicarbonate-based buffer solutions show better hemodynamic tolerance and reduce the incidence of cardiovascular adverse events compared to lactate-based CRRT solutions and hence are the preferred fluids for CRRT.<sup>159–161</sup> KDIGO guidelines suggest the use of bicarbonate-based fluids than lactate-based fluids for CRRT, especially in patients with circulatory shock, liver failure and lactic acidosis.<sup>8</sup> An increase in lactate concentration of  $>5$  mmol/L during CRRT indicates lactate intolerance.<sup>162</sup> However, lactate-based solutions may be used as a low-cost alternative to more expensive bicarbonate-based solutions in resource-limited conditions.

- **Fluid composition:** Electrolyte and divalent ion composition have a major impact on the electrolyte and divalent ion balance during CRRT. The CRRT fluids for dialysis and replacement should have the following compositions of electrolytes: Sodium 140 mmol/L, Potassium 0–4 mmol/L, Chloride 108–112 mmol/L, Calcium 1.5–1.75 mmol/L, Magnesium 0.5–0.75 mmol/L, and Glucose concentration of 0–15 mg/L.<sup>162</sup> Recently, phosphate-containing CRRT solutions are available which mitigate the occurrence of hypophosphatemia seen in CRRT, but they increase the risk of hypokalemia and metabolic acidosis.<sup>163</sup> Lactate-based fluid is sometimes used for dialysis in CRRT which contains a high concentration of Glucose up to 1.25 g/dL which may aggravate hyperglycemia in diabetic patients and hence are better avoided. The composition of fluids used for CRRT is shown in Table 11.
- **Physical properties of the solutions:** The lactate-based and buffer-free CRRT solutions have an acidic pH but greater stability whereas bicarbonate-based solutions have a physiologic pH. The use of dialysis and replacement fluids at room temperature can reduce the core body temperature by 2°C and a heat loss resulting in an energy loss of about 1000 kcal/day.<sup>164</sup> The cooling effect of CRRT has a beneficial effect on the hemodynamics<sup>165</sup> but the prolonged duration of hypothermia can affect cardiac function, immune system adversely and promote CRRT circuit clotting and hence is not desirable in critically ill patients.
- **Commercial solutions vs custom-made solutions:** Commercial solutions specifically made for CRRT are preferred over the solutions meant for intravenous administration such as 0.9% saline or ringer lactate or peritoneal dialysis such as 1.5% dextrose solution. However, in a situation wherein solutions specific to CRRT are not available either commercial solutions or custom-made solutions may be used for CRRT. Custom-made solutions involve admixture of multiple fluids and carry a risk of compounding error and a break in sterility and hence their use for CRRT should be discouraged.

**Table 11:** Composition of commercially available fluids used for CRRT

| Solution     | Use    | Na <sup>+</sup><br>(mmol/L) | K <sup>+</sup><br>(mmol/L) | Ca <sup>++</sup><br>(mmol/L) | Mg <sup>++</sup><br>(mmol/L) | Cl <sup>-</sup><br>(mmol/L) | HCO <sub>3</sub> <sup>-</sup><br>(mmol/L) | Lactate<br>(mmol/L) | Dextrose<br>(mg/dL) | PO <sub>4</sub> <sup>-</sup><br>(mmol/L) | Citrate<br>(mmol/L) |
|--------------|--------|-----------------------------|----------------------------|------------------------------|------------------------------|-----------------------------|---|---------------------|---------------------|--|---------------------|
| PrismaSol B0 | DF, RF | 140                         | 0                          | 1.75                         | 0.5                          | 109.5                       | 32  | 3.0                 | 0                   | 0  | 0                   |
| Dianeal      | DF     | 132                         | 0                          | 1.25                         | 0.25                         | 96                          | 0   | 40                  | 1200                | 0  | 0                   |
| PrismOcal    | DF     | 140                         | 0                          | 0                            | 0.5                          | 106                         | 32  | 0                   | 0                   | 0  | 0                   |
| Biphosphsyl  | RF     | 140                         | 0                          | 0                            | 0.75                         | 122                         | 22  | 0                   | 0                   | 1  | 0                   |
| Regiocit     | DF     | 140                         | 0                          | 0                            | 0                            | 86                          | 0   | 0                   | 0                   | 0  | 18                  |

DF, dialysis fluid; RF, replacement fluid

### Anticoagulation during RRT

- We recommend anticoagulant therapy in patients with AKI who require RRT, if there is no increased risk of bleeding. Patients, who are on systemic anticoagulation for comorbid conditions, do not usually require additional anticoagulation during RRT (1B).
- In patients with no clotting abnormalities, with no increased risk of bleeding, we recommend unfractionated heparin (UFH) during intermittent modalities of RRT. In the case of CRRT, we recommend RCA in centers with adequate expertise and experience with this strategy, and in centers lacking the expertise and experience for RCA, anticoagulation with UFH may be carried out (1B).
- In patients with impaired coagulation or increased risk of bleeding, we suggest either no anticoagulation or RCA during CRRT; an anticoagulant-free strategy for intermittent RRT (2C).
- We recommend the following options for anticoagulation in heparin-induced thrombocytopenia (HIT): direct thrombin inhibitors including Argatroban and Factor Xa inhibitors, such as Danaparoid or Fondaparinux (1A).

### Rationale

Anticoagulation is commonly used to prevent clotting of the extracorporeal circuit during RRT. Minor degrees of clotting in the fibers within the filter may reduce solute clearance while an extensive clot formation results in loss of the filter, circuit, and sequestered blood within the system. Furthermore, interruptions due to filter clotting lead to loss of efficacy of CRRT. Hence, anticoagulation is usually required in patients with AKI who undergo RRT.

Unfractionated heparin and RCA involving the infusion of sodium citrate into the inflow limb of the extracorporeal circuit have been used during RRT. Compared to systemic UFH, the use of RCA may prolong filter life and reduce the incidence of bleeding complications during RRT for AKI.<sup>166,167</sup> In a recent study, patients were randomized to receive RCA ( $n = 300$ ) with a target systemic blood ionized calcium level of 1.0–1.4 mg/dL or systemic UFH ( $n = 296$ ) to maintain aPTT between 45 and 60 seconds.<sup>168</sup> RCA resulted in a significantly longer filter life (47 vs 27 hours), although the 90-day all-cause mortality was not different (51.2 vs 53.6%). RCA was associated with fewer bleeding complications; however, the incidence of new infections was significantly higher. RCA requires a protocolized approach, the ready availability of laboratory support round the clock with diligent monitoring of acid-base and electrolyte status, including sodium, calcium, and magnesium. RCA may be safely carried out only in centers with sufficient experience with this modality of therapy.

RRT may be feasible without anticoagulation for short duration, intermittent RRT, and in the presence of impaired coagulation due to hepatic dysfunction, dilutional coagulopathy, or thrombocytopenia.<sup>169</sup> Patients with coagulopathies are at increased risk of bleeding with a higher propensity for clotting of the extracorporeal circuit. It is appropriate to commence RRT with an anticoagulant-free strategy with a focus on interventions that prolong filter life including free-flowing venous access, pre-filter delivery of replacement fluid, limitation of filtration fraction, use of a predominantly diffusive type of therapy, and maintenance of high blood flow rates. The use of RCA may be a viable option in this setting.

Heparin-induced thrombocytopenia (HIT) results from antibodies directed against platelet factor 4, resulting in platelet

activation leading to a prothrombotic state. Investigation for HIT must be carried out if repeated clotting of the extracorporeal circuit occurs. If HIT is suspected or proven, all heparin administration must be completely stopped including the use of flushes and “heparin locks.” Anticoagulation may be initiated using thrombin inhibitors like Argatroban or Bivalirudin,<sup>170</sup> or Factor Xa inhibitors like Danaparoid and Fondaparinux. Argatroban may be preferable in the absence of hepatic dysfunction as it has a short half-life and may be monitored by aPTT levels.

### RRT for Dyselectrolytemia

- We recommend high-efficiency RRT modality such as IHD or SLED when a rapid correction of electrolytes is needed in life-threatening emergencies (1B).
- We recommend that while RRT is performed, the rate of correction of chronic hypo and hypernatremia should not exceed the recommended rate of correction. In acute symptomatic dysnatremia, serum sodium can be corrected rapidly (1A).
- We suggest using RRT for the management of severe dysnatremia refractory to medical treatment with or without AKI (UPP).

### Rationale

Critically ill patients with AKI often present with several electrolyte and acid-base disturbances,<sup>171</sup> and RRT may be needed in life-threatening situations. Besides, RRT itself can trigger several electrolyte disturbances, which warrant a modification in the dialysis fluid and replacement fluid (RF) composition. A rapid correction is best achieved with high-efficiency RRT such as IHD and SLED whereas more sustained correction is achieved with CRRT.<sup>172</sup>

Rapid changes in serum sodium levels, during correction, can have adverse consequences and therefore requires close monitoring and attention. Hyponatremia and hypernatremia are often considered as mirror images, and basic principles for correction apply to both.<sup>173</sup> The preferred rate of correction should be between 4 and 6 mEq/L/day and not to exceed 12 mEq/L/day.<sup>173</sup>

Hyponatremic patients with  $SNa > 120$  mEq/L and hypernatremic patients with Serum Na (SNa)  $< 165$  mEq/L may be managed by SLED. In these cases, low blood flow rates (50–150 mL/minute), low dialysate flow rates (100–300 mL/minute), and a dialysis fluid with a difference of Dialysate Na (DNA) within 6–8 mEq/L from the SNa and a shorter duration (120–180 minutes) of SLED may be used.<sup>174</sup> SNa should be monitored frequently and SLED should be discontinued once targeted correction is achieved. CRRT may be preferred over SLED in severe hypo-/hypernatremia where the rate of change in SNa during therapy can be better controlled. Hemodynamically unstable patients with severe hyponatremia (SNa  $< 120$  mEq/L) are best managed by CRRT, using the commercially available dialysate and RF with a sodium concentration of 140 mEq/L and simultaneously transfusing 5% dextrose (D5W) solution post filter (volume to be calculated as a part of replacement fluid). The rate of D5W can be adjusted using the formula given in Figure 1A.<sup>128</sup> In hemodynamically unstable patients with hypernatremia (SNa  $> 165$  mEq/L), managed by CRRT, 3% saline can be used post filter as part of the RF (formula given in Figure 1B).<sup>128</sup> The effects of adding free water and 3% saline to modify the sodium concentration in RF are outlined in Table 12. Custom-made fluids may be used as RF; however, these are subject to human errors and not routinely recommended. SNa should be monitored at least 6-hourly while on CRRT.

$$\text{D5W rate} = \frac{140 - \text{target } [\text{Na}^+]}{140} \times \text{Xdesired clearance}$$

**A**

$$\text{3\% infusion rate} = \frac{\text{target } [\text{Na}^+] - 140}{(513 - 140)} \times \text{Xdesired clearance}$$

**B**

**Figs 1A and B:** (A) Formula for administering 5% dextrose (D5W) as replacement fluid (RF) to manage hyponatremia during CRRT; (B) Formula for administering 3% saline as replacement fluid (RF) to manage hypernatremia during CRRT

**Table 12:** Effect of addition of free water and 3% saline on the sodium concentration of replacement fluid in CRRT

| <i>To lower sodium concentration in RF</i>                    |     |      |      |      |      |
|---|-----|------|------|------|------|
| Volume of the addition of free water* added to 5 L of RF (mL) | 0   | 150  | 250  | 500  | 750  |
| Final volume of RF (L)  | 5   | 5.15 | 5.25 | 5.5  | 5.75 |
| Final sodium concentration of RF (mEq/L)                      | 140 | 136  | 133  | 127  | 122  |
| <i>To achieve higher sodium concentration in RF</i>           |     |      |      |      |      |
| Volume of the addition of 3% saline to 1 L RF (mL)            | 0   | 10   | 20   | 30   | 40   |
| Final volume of RF (L)  | 1   | 1.01 | 1.02 | 1.03 | 1.04 |
| Final Sodium concentration of RF (mEq/L)                      | 140 | 145  | 150  | 155  | 160  |

RF, replacement fluid; \*Free water in the form of distilled water or 5% dextrose

In case of life-threatening hyperkalemia, hemodialysis should be initiated with dialysate potassium of 0 or 2 mEq/L, along with other antihyperkalemic measures.<sup>128</sup> In the event of hemodynamic instability, SLED or CRRT can be initiated. Hypokalemia during CRRT or SLED for AKI can be prevented and corrected with dialysate potassium of 3–4 mEq/L.<sup>175</sup>

RRT in the form of hemodialysis with a dialysate calcium of 1.25 mmol/L for 3–4 hours can be considered in (1) hypercalcemia associated with AKI, cardiac failure, or life-threatening complications, and (2) refractory severe hypercalcemia (>14 mg/dL).<sup>176</sup> Serum calcium is to be measured toward the end of the RRT session and later, at 12–24 hours intervals, to determine the degree of rebound. RRT may be repeated if needed. A rapid correction of hypercalcemia may be achieved with zero calcium in dialysate, but this is preferably avoided for fear of adverse cardiovascular events.<sup>177</sup>

RRT in the form of hemodialysis with dialysate magnesium of 1 mEq/L should be used in symptomatic hypermagnesemia (associated with cardiac arrhythmias or respiratory muscle paralysis) in isolation or in association with AKI or CKD.<sup>128</sup>

#### RRT in Toxicology

- We recommend against the routine use of RRT based only on the dose of ingested toxin or serum drug level in the absence of signs of toxicity. RRT should be initiated where the benefit outweighs the risk of the procedure and associated cost (1C).
- We suggest discontinuing RRT upon clinical improvement and resolution of manifestations of toxicity (2C).
- We recommend IHD as the modality of choice for most dialysable toxins (1C).

#### Rationale

RRT has evolved over the last century as a viable and effective therapy for removal of toxins.<sup>178</sup> The first review in 1958, on the role of hemodialysis in acute poisoning, described the characteristics that classified a poison as dialysable, namely,

the molecular weight, protein binding, volume of distribution, solubility, and clearance.<sup>179</sup> Current treatment practices are based overwhelmingly on experience, rather than on high-quality evidence because of ethical concerns regarding RCTs in such conditions. The EXtracorporeal TReatment In Poisoning (EXTRIP) workgroup was created as a collaborative effort to bridge the gaps in knowledge and provide the clinician with evidence-based recommendations.<sup>180</sup>

The various techniques currently available for toxin removal include convection, diffusion, adsorption, separation, and centrifugation incorporated into different modalities.<sup>181</sup> IHD, which uses the principle of diffusion, is the most widely utilized RRT worldwide for toxin removal. The use of CVVH and CVVHDF has gained popularity in recent times especially in patients with hemodynamic instability and those with large molecular weight toxins. Hemoperfusion which works by drug adsorption has been the preferred modality for lipid-soluble and highly protein-bound toxins. However, the emergence of the newer high-flux dialysis membranes has diminished their advantage.

Primary stabilization and risk assessment are paramount before considering RRT in the acutely poisoned patient. Likewise, signs of toxicity should guide the clinician rather than absolute drug levels.<sup>182,183</sup> There is ample experience to recommend RRT for toxic Alcohol poisoning, Salicylate toxicity, Lithium overdose, Metformin, and Valproic acid toxicity. The EXTRIP workgroup has provided evidence-based recommendations for 16 toxins currently and is working on newer drugs.<sup>180</sup>

#### Weaning from RRT

- We recommend that weaning from RRT may be considered in AKI when the intrinsic capacity of the kidneys has increased to a degree sufficient enough to cope with the metabolic and fluid demands (UPP).
- We recommend that a spontaneous improvement in urine output from oliguric to nonoliguric state (UO >400 mL/day) or urine creatinine clearance of more than 15–20 mL/minute may be considered as reliable clinical parameters to consider weaning from RRT (1B).
- We suggest that withdrawal from RRT may be considered in case the deteriorating condition renders the continuation of RRT to be futile after a comprehensive deliberation with all involved in the care of the patient and family (UPP).

#### Rationale

It is desirable to wean patients from acute RRT in a timely manner to prevent dialysis-related complications, reduce the cost of hospitalization, and prevent delays in renal recovery. The intrinsic capacity of the kidneys is assessed by the urine output and measured glomerular filtration rate (GFR), and the metabolic demand is assessed by the degree of critical illness-related parameters, the serum concentration of Urea, and Creatinine, volume status, and acid-base status. Weaning is to be considered when there is progressive improvement in the demand to capacity ratio while on RRT.

The clinical decision to wean acute RRT is multidimensional, integrating several clinical, laboratory, and resource factors. There is a wide variation in clinical practice and often the decision is individualized.<sup>184</sup> Common indications for initiating weaning from acute RRT are an increase in urine volume (74%), normalization of pH (70%), volume status (55%), and serum concentrations of urea and creatinine (39%).<sup>185</sup>

Several small and retrospective trials have evaluated the predictors of successful weaning from RRT in AKI using a wide variety of parameters (Table 13). Among the several predictors of successful weaning from RRT studied in AKI, the volume of urine and GFR measured by urine creatinine clearance from a collection of 2–24 hours is the most consistent.<sup>184</sup>

Uchino et al. performed a post-hoc analysis of the BEST study, a large multicenter prospective observational study wherein patients ( $N = 529$ ) who survived AKI on CRRT were analyzed for predictors of successful weaning from CRRT.<sup>186</sup> The multivariate logistic regression analysis showed that the increased urine output, lower serum creatinine, shorter duration of CRRT, and absence of pre-existing CKD were the independent predictors of successful weaning from CRRT. A progressive urine output of more than 436 mL/day showed the highest sensitivity and specificity. They reported that the positive predictive value for successful weaning from RRT was 80.9% when a cut-off for urine output of 400 mL/day without diuretics and 87.9% when a threshold of diuretic-induced urine output of 2300 mL/minute was used. The use of diuretics diminishes the predictive ability of urine output as the predictor of successful weaning from RRT<sup>186</sup> and the use of diuretics to reduce the frequency of RRT was discouraged in the KDIGO guidelines.<sup>8</sup>

Recently, Tourneur et al. compared in a retrospective study, the protocol-driven weaning of RRT to individual physician-directed decision and found no difference in the duration of RRT in the two groups.<sup>187</sup> Moreover, algorithms are often not adhered to discontinue RRT in AKI.<sup>188</sup> There are scant available data to propose a simple algorithm to consider discontinuing of RRT in AKI.

Discontinuation of RRT may be considered in specific situations where continuing RRT is considered futile from the medical perspective. A decision to terminate RRT for the reason of futility should be considered after careful and extensive deliberation amongst all the stakeholders.

#### RRT and ECMO

- We suggest combining the use of RRT with ECMO in patients on ECMO having AKI, with CRRT as the preferred mode (UPP).
- We recommend an individualized approach with close monitoring of fluid and metabolic status for timely initiation of RRT with ECMO (UPP).
- We recommend against one technique over another (Integrated vs parallel system) for CRRT on ECMO; the choice should be based on local expertise and human resources (UPP).

#### Rationale

It is estimated that 25–68% of ECMO-treated patients need RRT. Data evaluating the combined use of RRT and ECMO are mainly derived from retrospective studies.

There is no robust evidence to suggest the use of one RRT modality over another. Patient factors, goals of treatment, and the

**Table 13:** Summary of studies to predict successful weaning from RRT in AKI

|  | Study design (N)                                | Criteria selected with the cut-off value            | Strength of prediction            |
|--|---|---|-----------------------------------|
| <b>Urine output (spontaneous)</b>      |   |   |                                   |
| Uchino et al. <sup>186</sup>           | Prospective, <i>post-hoc</i> analysis (N = 529) | Urine output >436 mL/day                            | Sn: 0.46, Sp: 0.81 AUROC: 0.85    |
| Aniort et al. <sup>189</sup>           | Retrospective, (N = 67)                         | Urine output >8.5 mL/kg/day                         | Sn: 0.89, Sp: 0.73 AUROC: 0.86    |
| Chen et al. <sup>190</sup>             | Prospective, (N = 78)                           | Urine output >695 mL/day                            | Sp: 0.3, Sp: 0.88 AUROC: 0.86     |
| Kim et al. <sup>191</sup>              | Prospective, (N = 89)                           | Urine output >1.26 mL/kg/hour                       | Sn: 0.6, Sp: 0.67 AUROC: 0.67     |
| Wu et al. <sup>192</sup>               | Retrospective, (N = 9)                          | Urine output >880 mL/day                            | Sn: 0.87, Sp: 1.0                 |
| <b>Urine output (diuretic-induced)</b> |   |   |                                   |
| Uchino et al. <sup>186</sup>           | Post-hoc analysis (N = 194)                     | Urine output >2300 mL/day                           | AUROC: 0.671                      |
| Yoshida et al. <sup>193</sup>          | Retrospective (N = 30)                          | Urine output >1720 mL/day                           | Sn: 0.72, Sp: 1.0 AUROC: 0.84     |
| <b>GFR measurement</b>                 |   |   |                                   |
| Stads et al. <sup>194</sup>            | Prospective, (N = 61)                           | 6-hour Urine CrCl >11 mL/minute                     | AUROC: 0.781                      |
| Frohlich et al. <sup>195</sup>         | Retrospective, (N = 53)                         | 2-hour CrCl >26.2 mL/minute                         | Sn: 0.75, Sp: 0.84<br>AUROC: 0.82 |
| Yoshida et al. <sup>193</sup>          | Retrospective, (N = 38)                         | Kinetic eGFR >20.58 mL/minute                       | Sn: 0.71, Sp: 0.92 AUROC: 0.87    |
| <b>Urine chemistry</b>                 |   |   |                                   |
| Thomsen et al. <sup>196</sup>          | Prospective, (N = 22)                           | Urine NGAL 1650 µg/L, 6 hours after discontinuation | Sn: 0.67, Sp: 91<br>AUROC: 0.81   |
| <b>Blood chemistry</b>                 |   |   |                                   |
| Chen et al. <sup>190</sup>             | Prospective, (N = 78)                           | Plasma NGAL <403 ng/mL                              | Sn: 0.86, Sp: 0.73                |
| Chen et al. <sup>190</sup>             | Prospective, (N = 78)                           | Serum creatinine <224 µmol/L (2.5 mg/dL)            | Sn: 0.83, Sp: 0.88                |
| Stads et al. <sup>194</sup>            | Prospective, (N = 61)                           | SCr D2/D0 ratio <1.41                               | AUROC: 0.819                      |
| Kim et al. <sup>191</sup>              | Prospective, (N = 89)                           | Cystatin-C 1.85 mg/L                                | Sn: 76, Sp: 0.63 AUROC: 0.74      |

N, the number of patients successfully weaned; Sn, sensitivity; Sp, specificity; AUROC, area under the receiver operating characteristic curve; Cr Cl, creatinine clearance; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; D, day; h, hour

experience of the center play a role in selecting the RRT modality. Hemodynamic instability in patients on ECMO often warrants a continuous mode that permits a slower and steady solute and water clearance.<sup>109,197</sup>

The optimal timing for initiation of RRT for patients on ECMO remains unclear. Fluid overload has been recognized as an independent risk factor for worse outcomes and duration of ECMO. Hence, it is an important trigger for initiation of RRT while on ECMO. Other indications include AKI, uremia, acidosis, prevention of fluid overload, and electrolyte disturbances.<sup>198</sup>

There are three main modalities of combining CRRT and ECMO—the parallel system, in-line hemofilter technique, and integration.<sup>197</sup> The advantages and disadvantages of each are summarized in Table 14.

A survey of 65 ECMO centers showed that 50.8% of centers exclusively use CRRT, 21.5% use an in-line hemofilter, and 23% use no RRT during ECMO.<sup>198</sup> A systematic review with limited data synthesis of 19 studies found that combining ECMO and CRRT in all the above methods was safe and effective to improve fluid balance and correct electrolyte disturbances.<sup>199</sup> A small retrospective study of 68 patients showed similar efficacy in parallel and integrated systems.<sup>200</sup>

## RESEARCH RECOMMENDATIONS FOR ISCCM AKI-RRT GUIDELINES

Due to paucity of available literature on many aspects of AKI and RRT in ICU, the steering committee have given a large number

of UPP recommendations, thereby implying that there are many opportunities to generate evidence. We are postulating few areas where research is highly recommended to come up with high-grade recommendations.

- Need to identify risk factors and recommend interventions to reduce incidence of AKI
- Need to identify parameters which can be used to monitor progression or improvement of AKI
- Optimal protein intake in the critically ill patient needs to be determined
- Need to have randomized controlled trials to identify the hemodynamic monitoring tools which influence outcomes
- Need to have RCTs between commercial fluids vs custom-based fluids for replacement/dialysate in CRRT to determine efficacy and safety
- Need to design an evidence-based protocol in deciding weaning off RRT

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**Table 14:** Advantages and disadvantages of main modalities of combining CRRT and ECMO

|               | <i>Parallel system</i>  | <i>In-line hemofilter technique</i>   | <i>Integrated system</i>  |
|---------------|---|---|---|
| Advantages    | <ul style="list-style-type: none"> <li>• No interference with either the systemic or ECMO hemodynamics</li> <li>• Ultrafiltration is controlled by the CRRT machine.</li> <li>• Mode of solute clearance not restricted</li> <li>• Precise fluid removal</li> <li>• Ability to provide CRRT independent of ECMO</li> <li>• No need for separate anticoagulation</li> <li>• Option of using a separate anticoagulation method to keep CRRT circuit patent</li> <li>• No need to involve the ECMO team when changing CRRT circuit</li> <li>• Can be considered when CRRT was being used before initiating ECMO</li> </ul> | <ul style="list-style-type: none"> <li>• Smaller priming volume of the external CRRT circuit</li> <li>• The simplest technique of RRT on ECMO</li> <li>• Low cost, ease of set up, use of less blood volume than a circuit to CRRT machine</li> <li>• Ability to generate large volumes of ultrafiltrate</li> </ul>   | <ul style="list-style-type: none"> <li>• Enables precise control of the blood flow in the CRRT circuit with appropriate monitoring of the TMP and exact fluid balancing</li> <li>• Mode of solute clearance not restricted</li> <li>• Control of ultrafiltration</li> <li>• No need for separate vascular access</li> <li>• No need for separate anticoagulation</li> </ul> |
| Disadvantages | <ul style="list-style-type: none"> <li>• Need for separate vascular access</li> <li>• Increased difficulty caring for a patient with two separate extracorporeal circuits</li> <li>• Higher extracorporeal blood volume</li> </ul>  | <ul style="list-style-type: none"> <li>• Lacks TMP monitoring</li> <li>• Requires additional IV pump to control UF- often inaccurate</li> <li>• Requires measurements of UF volume using a balance or a volumetric measuring device</li> <li>• UF error &gt;800 mL</li> <li>• Limited solute clearance</li> <li>• Requires external pumps for fluid replacement and dialysate if indicated</li> </ul> | <ul style="list-style-type: none"> <li>• Exposure of CRRT machine to pressures outside the safety range</li> <li>• Risk of air entrapment</li> <li>• Flow turbulence and risk of hemolysis</li> <li>• Risk of thrombus formation on the additional connectors</li> <li>• Generation of shunt within ECMO circuit</li> </ul>   |

ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; TMP, transmembrane pressure; UF, ultrafiltration

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