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Non-dialytic and dialytic management of acute kidney injury

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INTRODUCTION

Optimal management of acute kidney injury (AKI) requires close collaboration among primary care physicians, nephrologists, hospital and intensive care specialists, and other subspecialists participating in the care of the patient. With patients who have been diagnosed with an AKI, management is primarily supportive. Patients with AKI should generally be hospitalized unless the condition is mild and is the result of an easily reversible cause, such as dehydration. The key to management is assuring adequate renal perfusion by achieving and maintaining hemodynamic stability and avoiding hypovolemia. Both the clinical assessment of intravascular volume status and avoidance volume overload during fluid administration may be difficult. In these cases, measurement of central venous pressures, or more invasive hemodynamic parameters, may be helpful in an intensive care unit (ICU) setting [1].

The first and second paper in this series described the definition and epidemiology of AKI [2] and the approach to the patient with presumed AKI [3]. This paper describes the non-dialytic and dialytic management of patients with AKI.

The non-dialytic management of AKI is discussed in more detail in several reviews [4-7], clinical practice guidelines [8], and chapters in recent textbooks of nephrology [9] and Critical Nephrology [10]. Recent papers covering some of these aspects have focused on more specific methods of managing AKI in low-income countries [11, 12].

FLUID THERAPY AND DIURETICS IN AKI [13]

There is a direct link between fluid overload and mortality in critically ill patients with AKI. Fluid overload is usually defined as a >10% increase in body weight [13-15]. Expansion of extracellular fluid volume is an inevitable consequence of diminished salt and water excretion in oliguric or anuric individuals. Milder forms are characterized by body weight gain, physical signs of pulmonary congestion, raised jugular venous pressure, and peripheral edema. Continued volume expansion may precipitate life-threatening pulmonary edema. Hypervolemia is often the consequence of the administration of multiple intravenous medications and enteral or parenteral nutrition [13]. Hypo-osmolality and hyponatremia, which can lead to cerebral edema and neurologic abnormalities such as seizures, can be provoked by excessive administration of free water. This excessive fluid administration comes about either through ingestion and nasogastric administration, or as hypotonic saline or isotonic dextrose solutions after the metabolization of the dextrose [16].

The fluids available in Rwanda include crystalloids (isotonic saline, Ringer's lactate), colloids (haemacel®, human albumin), and blood products.

If fluid resuscitation is required because of intravascular volume depletion, isotonic solutions (e.g., normal saline) are preferred over colloid solutions (e.g., dextrans, hydroxyethyl starches, and albumin). In a meta-analysis, [17] hydroxyethyl starch was associated with an increase in mortality, AKI incidence, and use of renal-replacement therapy (RRT). Therefore, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have issued warnings against the use of hydroxyethyl starch solutions in patients who are critically ill, and their use is now no longer recommended [7]. Hyperchloremia induced by non-physiologic levels of chloride in 0.9% saline solutions might have adverse effects on renal function and on acid-base homeostasis by inducing mild hyperchloremic acidosis. In observational studies [18], a chloride-restrictive strategy of infusing more "balanced" solutions in patients who were critically ill was associated with reduced incidence of AKI and the need for RRT. However, a recent prospective trial could not confirm these results in a general ICU population [19].

In patients with septic and non-septic shock, a reasonable goal is achieving a mean arterial blood pressure of >65 mmHg. This may

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require the additional use of vasopressors (i.e., norepinephrine) in patients who have persistent hypotension, despite adequate fluid therapy [20]. Renal-dose dopamine is associated with poorer outcomes in patients with AKI and is no longer recommended [21]. Cardiac function can be optimized as needed with positive inotropes, or afterload and preload reduction [22].

In Rwanda, loop diuretics are often mistakenly used to force diuresis in AKI patients. However, this practice often worsens the renal outcome, especially in hypovolemic patients who need fluid replacement therapy and therefore improve their urine output rather than diuretics. As discussed in the KDIGO guidelines for AKI [8], the leading indication for the use of IV diuretics in AKI patients either as a bolus or as a continuous infusion is the management of volume overload. It is important to note that diuretics do not improve morbidity, mortality, or renal outcomes, and should not be used to prevent or treat AKI in the absence of volume overload [23]. A recent randomized trial confirmed that furosemide did not reduce the rate of worsening AKI, improve recovery, or reduce the need of RRT. Instead, it was associated with greater electrolyte abnormalities [24].

Routine administration of mannitol to oliguric patients is not recommended and, when administered to severely oliguric or anuric patients, mannitol may trigger the expansion of intravascular volume, pulmonary edema, and severe hyponatremia caused by an osmotic shift of water from the intracellular to the intravascular space [8].

Fluid management in severe sepsis and septic shock

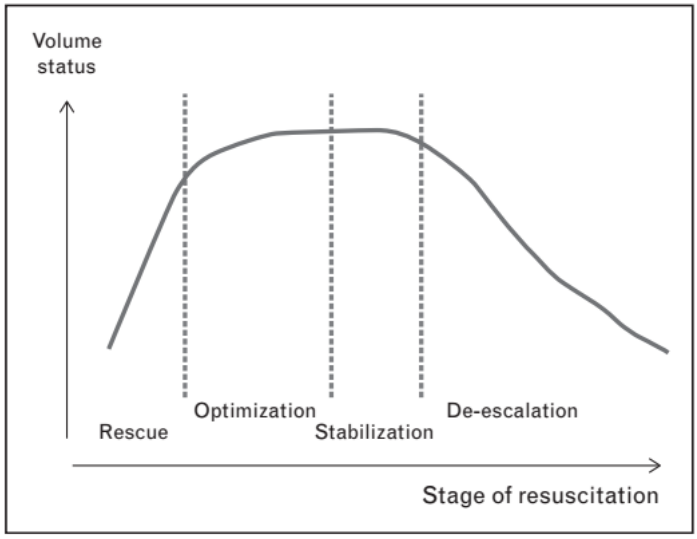
A recent in-depth review [25] on AKI in sepsis discusses in detail the problems of fluid administration in this setting. It should, however, be noted that sepsis-associated AKI is frequently a life-threatening illness requiring management of two simultaneous problems: source control of sepsis by antibiotics and eventual surgical approach of the local infection source, which is accompanied by intensive monitoring and multi-organ support in the ICU [26]. Whilst early fluid resuscitation has long been a standard treatment in the management of hypotensive patients, protocolized hemodynamic management strategies have become widely used since the landmark study of Rivers et al. who demonstrated that early goal-directed therapy (EGDT) with predefined physiologic endpoints might prevent organ failure and improve the outcome of patients with septic shock[27]. Of note, the EGDT protocol required rapid use of fluids during the first 6 hours of treatment (4981 ± 2984 mL compared to 3499 ± 2438 mL in the standard therapy group), while the total volume administered during the first 72 hours was not different (13358 ±7729 mL versus 13443 ±6390 mL).

As detailed in Bellomo et al. [25], later studies failed to show the benefit of the EGDT approach for reducing AKI, utilization of RRT, or kidney recovery. Also, three important randomized, controlled trials (ProMISe [28], ProCESS [29], and ARISE [30] trials) demonstrated no difference in mortality or improved renal outcomes with EGDT. As further explained in the Bellomo paper, fluid bolus therapy combined with the frequent presence of oliguria in septic AKI is likely to lead to fluid accumulation in septic patients. This was also associated with adverse outcomes and increased mortality in several studies [25].

Overall, the relationship between volume status and the development of complications resembles a U-shaped curve. This indicates that there is only a fine margin between hypovolemia and overhydration, both of which will lead to complications [13]. As a consequence, hydration status must be carefully monitored and infusion strategies closely adapted to a patient's needs [31].

A new model of fluid therapy, schematically depicted in Figure. 1, was established by the Acute Dialysis Quality Initiative (ADQI) [32]. The new model is based on expert consensus and consists of 4 phases of fluid therapy in AKI patients. The phases of the fluid model are the Rescue phase, Optimization phase, Stabilization phase, and the De-escalation phase.

Figure 1. Patient's volume status at different stages of resuscitation, taken from [32].



With the model, fluid boluses are only administered during the acute life-threatening hemodynamic instability, like a patient in decompensated (septic) shock. Once the patient is no longer at risk for acute decompensation, additional fluid is titrated carefully using fluid challenges to optimize end-organ perfusion and cardiac output. Once the patient has stabilized, fluids are minimized to achieve a fluid steady state. The de-escalation phase then aims to remove excess fluid and minimize additional harm [32].

Table 1 summarizes the surviving sepsis campaign care bundles that are recommended for a patient admitted with suspected sepsis and/or septic shock [33, 34].

Table 1 Summary of the Surviving Sepsis Campaign Care bundles [31, 32]

Time critical	Actions in care bundle
To be completed within 3 hours	Measure lactate level Obtain blood cultures before administration of antibiotics Administer broad spectrum antibiotics Administer 30 ml/kg crystalloids for hypotension or lactate ≥4 mmol/L
To be completed within 6 hours	Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial blood pressure ≥ 65 mm Hg In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L Measure central venous pressure (CVP)* Measure central venous oxygen saturation ($ScvO_2$)* Remeasure lactate if initial lactate was elevated*

**Targets for quantitative resuscitation included in the guidelines are CVP ≥ 8 mmHg, $ScvO_2$ of ≥ 70%, and normalization of lactate*

This care bundle recommends initial resuscitation with fluid loading, early administration of broad-spectrum antibiotics, and application of vasopressors to reverse hypotension that does not respond to initial fluid with a mean arterial pressure target of at least 65 mmHg. However, for patients with atherosclerosis or previous hypertension, a higher blood-pressure target (80 to 85 mmHg) may be better [20].

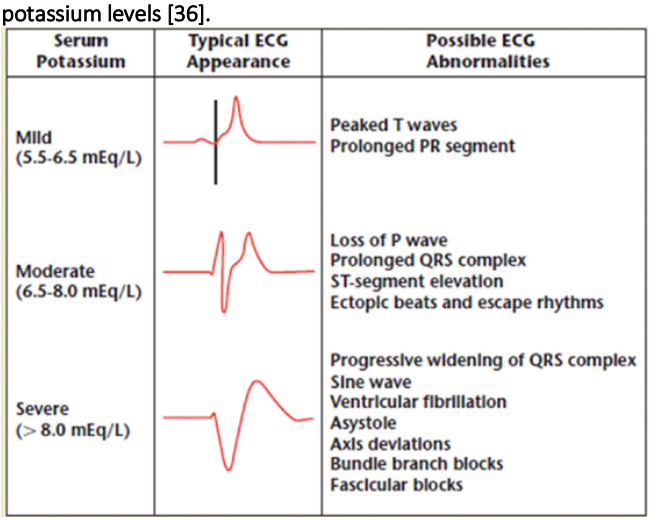
Electrolyte and acid-base disturbances in AKI

A detailed discussion of electrolyte and acid-base disturbances can be found in Joerres et al. [35]. Particular attention should be paid to the prevention and treatment of electrolyte imbalances (e.g., hyperkalemia, hyperphosphatemia, hypermagnesemia, hyponatremia, hypernatremia, metabolic acidosis) in the patient with established AKI.

Hyperkalemia

The most dangerous electrolyte disturbance is severe hyperkalemia. Hyperkalemia is defined as potassium levels of 6.5mEq per L (6.5 mmol/) or higher, or less than 6.5 mmol/L in the presence of electrocardiographic changes typical of hyperkalemia (e.g., tall, peaked T waves) (Figure 2)

Figure 2: ECG changes in hyperkalemia - The classical changes in the electrocardiogram related to progressively higher levels of extracellular potassium levels [36].



Serum potassium concentrations at ICU admission, as well as velocity and duration of hyperkalemia, are strong predictors of all-cause mortality with a significant risk gradient across serum potassium strata [37, 38]. This is because hyperkalemia is associated with worse disease conditions. However, data showing an association between dismal outcome and hyperkalemia are largely retrospective [38].

The emergency treatment of severe hyperkalemia has recently been reviewed in two publications [39, 40]. It should be emphasized that the "classical" emergency treatment of life-threatening hyperkalemia (infusions of calcium, insulin, and dextrose, and β_2 agonists) are only temporary measures since all are acting either by inhibiting cardiac potassium toxicity (calcium) or by the redistribution of potassium into the intracellular fluid. None of these measures contribute to the enhanced elimination of potassium from the body. The only intervention that eliminates potassium from the body is gastrointestinal binding of potassium or the initiation of RRT.

Calcium gluconate (10 mL of 10% solution infused intravenously over five minutes) is used to stabilize the cardiac membrane and reduce the risk of arrhythmias when there are electrocardiographic changes showing hyperkalemia. The onset of intravenous calcium is almost immediate, but the duration of effect is only 30 to 60 minutes.

In severe hyperkalemia, an initial bolus of 10 units of regular insulin usually is given to induce a shift of potassium into cells. Insulin should be given with glucose, usually 50 mL of 50% dextrose (25 g of glucose), to avoid hypoglycemia. Glycemia should be monitored closely after the insulin bolus. A 10% dextrose infusion also may be given subsequently (75 mL per hour) to prevent hypoglycemia. Regular insulin with glucose/dextrose alone, or a combination of nebulized beta-2-agonist (e.g., albuterol 10–20 mg, salbutamol 20 mg), can be used as a single dose to shift potassium intracellularly. One potential approach to dosing a 70 kg subject (with weight adjustment of dosages for others) is a 6 unit loading dose of short-acting insulin followed by an insulin infusion of 20 units/h. This is together with 60 gm of glucose per hour, which might be preferable to the standard dosing (usually insulin 10 units/glucose 25 g) because of a lower potential for hypoglycemia.
Insulin and glucose carry a high risk of hypoglycemia after 1 hour, with several case reports of life-threatening and even fatal

hypoglycemia and require close monitoring. Insulin and glucose act within 15 minutes, peak around 30 to 60 minutes and have a total duration of four to six hours (for more details see reviews [39, 40]).

In patients without electrocardiographic evidence of hyperkalemia, calcium gluconate is not necessary. However, sodium polystyrene sulfonate (Kayexalate®), or one of the newer oral potassium binders (patiromer or sodium zirconium cyclosilicate (ZS-9), can be given to lower potassium levels gradually [39]. The efficacy of polystyrene sulfonate (SPS) is, however, uncertain, and the osmotic diarrhea induced by co-administration with sorbitol (or cathartic agents that cause secretory diarrhea) has been proposed as the primary mechanism by which potassium is lowered. It is not ideal for administration in the emergency setting because of it's delayed and highly variable onset. It should be noted that Kayexalate® has been associated with several gastrointestinal complications and some reported cases have been fatal [41].

Dietary intake of potassium should also be restricted. Of additional note, the most important medication class linked to hyperkalemia are inhibitors of the renin-angiotensin-aldosterone system (RAAS), such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, and mineralocorticoid receptor blockers [39].

Metabolic acidosis

Metabolic acidosis is not usually treated unless serum bicarbonate concentration falls below 15mmol/L or arterial pH <7.2. More severe acidosis is corrected by oral or intravenous sodium bicarbonate. Estimates of bicarbonate deficit guide initial rates of replacement and adjusted after that according to serum levels. One should remember that the administration of bicarbonate to an acidotic patient can cause an increase in intracellular acidosis [42]. Patients are monitored for complications of sodium bicarbonate administration such as hypervolemia, metabolic alkalosis, hypocalcemia, and hypokalemia. Acidosis can be particularly severe when other mechanisms increase endogenous production of hydrogen ions (e.g., diabetic or fasting ketoacidosis, lactic acidosis complicating generalized tissue hypoperfusion, liver disease, sepsis, or metabolism of ethylene glycol or methanol). From a practical point of view, the presence of persistent severe metabolic acidosis is an absolute indication for initiating emergency dialysis. However, no studies exist where a clearly defined threshold for initiation of RRT in AKI patients with metabolic acidosis was associated with improvement of clinically relevant outcomes. Overall, in the absence of severe respiratory acidosis, intractable metabolic acidosis with a pH <7.15 is a frequently quoted indication for RRT.

Hypo and hyperphosphatemia

As explained by Joerres et al. [35], hypophosphatemia is rare. However, some patients are at higher risk. In the ICU, patients undergoing continuous RRT may develop a severe decrease in phosphate. In this setting, phosphate should be monitored on a regular basis and supplemented if needed. In general, mild hypophosphatemia can be managed with oral supplements. Severe symptomatic hypophosphatemia (<0.5 mmol/L) requires an IV application of phosphate. The extent of the possible phosphate deficit is unpredictable, and repletion therapy must be empiric. In the ICU, a single dose of 15–30 mmol over 2 hours, or a dose of up to 0.08 mmol/kg body weight, is considered safe and have been well tolerated [43]. One should be cautious, however, when the serum calcium is grossly elevated due to the risk of soft tissue calcification. Calcium and phosphate repletion must be strictly separated, as precipitation may trigger anaphylactic reactions. Careful monitoring of phosphate and prevention of hypophosphatemia is therefore much safer than intravenous infusions.

Hyperphosphatemia is a common condition in patients with AKI and is a biomarker of disease severity and predictor of outcome in AKI. It is likely due to decreased phosphate removal and secondary hyperparathyroidism as a result of reduced kidney function [44]. Mild hyperphosphatemia is an almost invariable complication of AKI. Severe hyperphosphatemia may develop in highly catabolic patients or following rhabdomyolysis, hemolysis, or tumor lysis. Metastatic deposition of calcium phosphate can lead to hypocalcemia, particularly when the product of serum calcium (mg/dL) and phosphate (mg/dL) concentrations exceed 70. Other factors that contribute to hypocalcemia include tissue resistance to the actions of parathyroid hormone and reduced levels of 1.25 hydroxyvitamin D. Hypocalcemia is often asymptomatic but can cause perioral paresthesia, muscle cramps, seizures, hallucinations and confusion, and prolongation of the QT interval and nonspecific T-wave changes on electrocardiography [45]. Acute phosphate nephropathy is a clinical, pathological entity characterized by acute and subsequent chronic renal failure following exposure to oral sodium phosphate (OSP) bowel purgatives. Several case reports and a comprehensive editorial have described this entity [46].

Hyperphosphatemia is usually controlled by restriction of dietary phosphate and by oral aluminum hydroxide or calcium carbonate, which reduce gastrointestinal absorption of phosphate. Hypocalcemia does not usually require treatment unless severe, as it may occur with rhabdomyolysis, pancreatitis, or following administration of bicarbonate.

One should, however, understand that in the polyuric phase of AKI, potassium and phosphorus may be depleted. Patients may then require dietary supplementation and intravenous replacement of both electrolytes. Similar depletions may occur during RRT.

Except for tumor lysis syndrome [47], hyperuricemia is typically mild [<890 mol/L (< 15 mg/dL)] and does not require intervention.

Other therapeutic interventions [9]

The objective of nutritional management during the maintenance phase of ARF is to provide sufficient calories to avoid catabolism and starvation ketoacidosis while minimizing the production of nitrogenous waste. Dietary protein should be restricted to approximately 0.6 g/kg per day of high biologic value protein (rich in essential amino acids) and to provide most calories in the form of carbohydrates (approximately 100 g daily). Nutritional management is more straightforward in non-oliguric patients and

following institution of dialysis. Improvement of prognosis with parenteral hyperalimentation has yet to be demonstrated in controlled trials.

As summarized by Vanmassenove et al [7], intensity of glycemic control in the perioperative phase and in patients in the ICU has been a matter of controversy. Early single-center studies showed that glycemic control reduced mortality and incidence of AKI, but later multicenter trials did not confirm these findings [48]. Because long-term benefits of strict glycemic control are offset by the risk of hypoglycemia, modest glycemic control (achieving serum glucose concentration of 8.3–10.0 mmol/L) is the preferred strategy.

Besides the typical form of microangiopathic haemolytic anemia that is a characteristic of all thrombotic microangiopathies [49], other forms of anemia develop rapidly in ARF and are usually mild and multifactorial in origin. Contributing factors include impaired erythropoiesis, hemolysis, bleeding, hemodilution, and reduced red blood cell survival time. Mild gastrointestinal bleeding is common in AKI (10-30%) and is usually due to stress ulceration of gastric or small intestinal mucosa. Regular doses of antacids appear to reduce the incidence of gastrointestinal hemorrhage significantly and may be more effective than H_2 antagonists or proton pump inhibitors.

Anemia may necessitate blood transfusion or administration of recombinant human erythropoietin if severe or if recovery is delayed.

Prolongation of the bleeding time and leukocytosis are also common. Common contributors to the bleeding diathesis include mild thrombocytopenia, platelet dysfunction, and/or clotting factor abnormalities (e.g., factor VIII dysfunction). This in contrast to leucocytosis, which usually reflects sepsis, a stress response, or other concurrent illness. Uremic bleeding usually responds to desmopressin, correction of anemia, estrogens, or dialysis [50].

Infection is a common and serious complication of AKI, occurring in 50% to 90% of cases and accounting for up to 75% of deaths (for review see [9]). It is unclear whether patients with AKI have a clinically significant defect in host immune responses or whether the high incidence of infection reflects repeated breaches of mucocutaneous barriers (e.g., intravenous cannulae, mechanical ventilation, bladder catheterization). Febrile patients must be investigated aggressively for infection and may require treatment with broad-spectrum antibiotics while awaiting identification of specific organisms.

Meticulous care of intravenous cannulas, Foley catheters, and other invasive devices is mandatory. Unfortunately, prophylactic antibiotics have not been shown to reduce the incidence of infection in these high-risk patients [9].
Cardiopulmonary complications of AKI include arrhythmias, myocardial infarction, pericarditis and pericardial effusion, pulmonary edema, and pulmonary embolism.

Doses of all drugs that are excreted by the kidney must be adjusted for the degree of renal impairment [9] and, in particular, the pharmacokinetic characteristics of potentially nephrotoxic drugs should be noted.

Renal replacement therapies (RRTs) in AKI

Renal replacement therapy (RRT) helps to remove fluid overload and waste products until the preserved kidney function is restored.

RRT modalities used in the treatment of the patients with AKI include conventional intermittent hemodialysis (IHD), various continuous RRT (CRRT) modalities, "hybrid" modalities that combine aspects of both conventional IHD and CRRT like slow low-efficiency daily dialysis (SLEDD), prolonged intermittent replacement therapy (PIRRT), and peritoneal dialysis (PD).

Hemodialysis modalities

Recent reviews on the different RRT modalities in AKI [51-53] are available. As mentioned in the first paper in this series [2], RRT in Rwanda is an emerging treatment where peritoneal dialysis is offered in only one of the six dialysis centers.

IHD is less expensive and has similar efficacy when compared to CRRT. If indications warrant, hemodialysis can be performed daily (called SLEDD) and can be run for extended treatment times (6–10 hours). SLEDD, alternatively called PIRRT, is associated with a considerable reduction in cost. Although the logistical mechanics regarding the use of IHD and SLEDD likely differ across the world, they are typically delivered by hemodialysis nurses under the supervision of a nephrologist. This is in contrast to CRRT, which may be delivered by ICU nursing staff [54].

SLEDD is a slower dialytic modality that is run for prolonged periods using conventional hemodialysis machines with lower blood pump speeds (e.g., 200 ml/min) and dialysate flow rates (e.g., 100–300 ml/min) for 8–16 hours daily. SLEDD combines advantages of CRRT and IHD and facilitates improved hemodynamic stability with gradual solute and volume removal, similar to CRRT. It also utilizes the less expensive technology of online dialysate generation intrinsic to conventional IHD. Because SLEDD can be performed intermittently on per the needs of the patient, they allow the scheduling of required diagnostic and therapeutic procedures without interruption of therapy. Thus far, PIRRT has provided hemodynamic control comparable to CRRT[54].

Several studies have demonstrated equivalent outcomes with IHD and CRRT. The choice of intermittent or continuous therapy is currently based on local experience and availability of therapies [55]. Ideally, the dialysis prescription (blood and dialysate flow, dialysate composition and temperature, ultrafiltration rate, anticoagulation) should be tailored to the patient's needs, which may change daily in the critically ill. In the RENAL Trial [56], patients were randomized to continuous venovenous hemodiafiltration (CVVHDF) at 25 or 40 ml/kg per hour. In the ATN Study [57], patients transitioned between modality, receiving IHD/sustained low-efficiency dialysis with a target Kt/Vurea of 1.2–1.4 per treatment. This is administered either three or six times per week when hemodynamically stable and CVVHDF at 20 or 35 ml/kg per hour when hemodynamically unstable. In both studies, more intensive therapy was not associated with

Table 2 Currently accepted "conventional" or "absolute" indications for initiation of renal replacement therapy [65]

Parameter	Definition
Hyperkalemia	Serum potassium ≥6 mmol/l, or rapidly rising potassium, or refractory to standard supportive medical management
Metabolic Acidosis	pH ≤ 7.15
Uremia	Urea > 36 mmol/l (equals BUN=100.8 mg/dl, blood urea=216mg/dl)
Oliguria or anuria	Urine Output < 0.3ml/kg/h for ≥ 24 hours or anuria for ≥ 12 hours
Fluid Overload	Pulmonary edema not responding to diuretics and defined by the presence of all of the following factors: *>10% fluid accumulation (cumulative fluid balance/baseline weight > 10%), * oliguria (urine output < 0.5 ml/kg/h for ≥12 hours) and * severely impaired oxygenation (PaO2/FiO2<200 indicated by respiratory Sequential Organ Failure Assessment (SOFA) score ≥3)

improved survival or recovery of kidney function. Current guidelines recommend prescribing a CRRT dose of 25 ml/kg per hour in order to provide an effective dose of at least 20 ml/kg per hour [8, 58]. In all these studies, the dose of dialysis has been based on clearance of small molecules and did not include fluid balance. The RENAL trial showed that survival rates were improved by maintaining a negative fluid balance. Some studies suggest that CRRT techniques are associated with improved renal recovery. When intensive regimens are used, dosing of medications, such as antibiotics, should be adjusted.

Since intermittent hemodialysis is available in 6 Rwandese centers, there is no reason why an efficient and slow dialysis technique like SLEDD should not be applied whenever there is an indication for acute RRT and PD is either unavailable or contraindicated (like after abdominal surgery or for ventilated patients).

Peritoneal dialysis in AKI

In high-income countries acute peritoneal dialysis (PD) in adult critically ill, notably septic AKI patients, is rarely used. This is different in young children and in low-income countries where PD is more manageable to initiate. This easier initiation comes from its technical simplicity or because equipment for extracorporeal techniques is lacking [59]. PD has the advantage of low cost, easy and safe catheter placement, lack of need for anticoagulation, and gentle, continuous fluid and solute removal. Several RCTs have compared acute PD with hemodialysis modalities in AKI patients. Recent RCTs found similar survival between PD and daily intermittent HD [60-63]. The major complications of acute PD are peritonitis and technical complications with the acute catheter. Although theoretically less expensive than HD, the often high import costs for the peritoneal dialysis fluids make acute PD not feasible in low-income countries [62]. The Sustainable Kidney Care Foundation, together with industry, universities, and funding organizations, tries to establish PD programs for AKI in African countries with a particular focus on treating children and women of childbearing age [64]

The timing of initiation of RRT.

It is somewhat surprising that for most of the criteria, hard evidence to support their validity is lacking. It is especially surprising since they are based on incorrect extrapolations from observational studies that mix cause and consequence. Although the early initiation of RRT was reported to be beneficial in critically ill patients with AKI, this might expose patients to unnecessary RRT. The decision to start RRT is unequivocal in the presence of life-threatening AKI complications, but in their absence, the optimal timing of dialysis start for AKI remains uncertain., especially since two recently published randomized trials, the ELAIN trial [66] and the AKIKI trial [67], showed seemingly opposite results.

As recently outlined in an editorial [68] discussing these two studies, early initiation of RRT in AKI could improve outcomes by limiting fluid overload and organ injury and, in case of sepsis, by removing inflammatory mediators. A recent systematic review demonstrated that this last strategy is of no benefit [69]. However, adopting an early RRT initiation strategy in AKI might increase the risk for unnecessary RRT in a number of patients exposing them to potential technical complications of dialysis, anticoagulation and inadequate dosing of antibiotics, and a potential delay in renal recovery.

The single-center ELAIN trial [66] demonstrated a marked survival benefit in post-cardiac surgery patients with either severe sepsis or refractory fluid overload by initiating continuous RRT within 8 hours of reaching KDIGO Stage 2 AKI. The "delayed" group initiated RRT within 12 hours of reaching Stage 3 AKI. A significantly lower 90-day mortality rate was observed in the early group versus the delayed group. Since, in the delayed group, almost 75% of patients were diagnosed with fluid overload or worsening pulmonary edema before randomization, ELAIN investigated the effect of delaying dialysis in patients who needed it. Severe pulmonary edema is universally recognized as an absolute indication for emergent RRT. The fact that over 90% of patients in the delayed group eventually received dialysis underscores this. It is thus not surprising that ELAIN concluded that early start improved patient outcome.

The multicenter Artificial Kidney Initiation in Kidney Injury study (AKIKI) [67] randomly assigned patients in 31 French ICUs to receive RRT in either an immediate (early) or a delayed strategy. Both patient groups had KDIGO Stage 3 AKI and were receiving invasive mechanical ventilation, vasopressors, or both. Patients with established criteria to start dialyses, such as severe hyperkalemia or pulmonary edema, were excluded and started RRT immediately. In the early group, RRT was started within 6-hours of documenting Stage 3 AKI. The delayed group started

whenever one of the predefined criteria was met. AKIKI showed no superiority for early initiation of RRT and avoided unnecessary RRT in 49% of the delayed group (vs. only in 9% in the ELAIN trial). Recovery of residual diuresis was faster in the delayed group while catheter-related bloodstream infections were higher in the early-strategy group.

The actual opinion is that "early" initiation of RRT, compared to "late initiation," at least in critically ill patients, does not result in reduced mortality or any other relevant outcome measure. In the absence of life-threatening conditions, in which case dialysis should not be delayed, an “expectation Armata” approach seems justified. There is no convincing evidence that, in the absence established criteria, early start of dialysis improves outcome.

REFERENCES

[1] M. Rahman, F. Shad, and M. C. Smith, "Acute kidney injury: a guide to diagnosis and management," (in eng), *Am Fam Physician,* vol. 86, no. 7, pp. 631-9, Oct 1 2012.

[2] V. I. Nsengiyumva, Grace; Lameire, Norbert, "Definition and epidemiology of acute kidney injury," *Rwanda Medical journal,* vol. 75, no. 2, pp. 17-23, 2018.

[3] I. G. Nsengiyumva V, Lameire N, "Approach to the patient with presumed AKI," *Rwanda Medical Journal,* REview vol. 75, no. 4, p. in press, 2018.

[4] R. Bellomo, J. A. Kellum, and C. Ronco, "Acute kidney injury," (in eng), *Lancet,* vol. 380, no. 9843, pp. 756-66, Aug 25 2012.

[5] N. Lameire, W. Van Biesen, and R. Vanholder, "Acute renal failure," (in eng), *Lancet,* vol. 365, no. 9457, pp. 417-30, Jan 29-Feb 4 2005.

[6] A. S. Levey and M. T. James, "Acute Kidney Injury," (in eng), *Ann Intern Med,* vol. 167, no. 9, pp. Itc66-itc80, Nov 07 2017.

[7] J. Vanmassenhove, J. Kielstein, A. Jorres, and W. V. Biesen, "Management of patients at risk of acute kidney injury," (in eng), *Lancet,* vol. 389, no. 10084, pp. 2139-2151, May 27 2017.

[8] "KDIGO Clinical Practice Guidelines in Acute Kidney Injury," *Kidney International supplement,* vol. 2, no. 1, pp. 1-138, 2012.

[9] A. Joerres, Harper,D., Oppert,M., "Non-dialytic management of the patient with acute kidney injury.," *Oxford Textbook of Clinical Nephrology-4th edition,* vol. 1; chapter 228, pp. 1943-1950, 2015.

[10] B. R. Ronco C, Kellum JA, Ricci Z., Ed. *Critical Care Nephrology,*, Third ed. Philadelphia: Elsevier, 2018.

[11] V. Kher, Srisawat N.,Noiri,E.,Gharbi,M.B.,Shetty,M.S.,Yang,L.,Bagga,A., Chakravarthi,R.,Mehta,R., "Prevention and therapy of acute kidney injury in the developing world.," *Kidney Int Rep. the Acute Disease Quality Initiative (ADQI) Consensus Group,* 2017.

[12] B. A. Mehta RL, Patibandla R, Chakravarthi R., "Detection and Management of AKI in the Developing World: The 18th Acute Disease Quality Initiative (ADQI) International Consensus Conference," *Kidney Int Reports,* 2016.

[13] A. Joerres, Harper,D., Oppert, M., "Fluid overload," *Oxford Textbook of Clinical Nephrology-4th edition,* vol. 1,Chapter 229, pp. 1951-1954, 2015.

[14] J. Bouchard *et al.*, "Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury," (in eng), *Kidney Int,* vol. 76, no. 4, pp. 422-7, Aug 2009.

[15] D. Payen, A. C. de Pont, Y. Sakr, C. Spies, K. Reinhart, and J. L. Vincent, "A positive fluid balance is associated with a worse outcome in patients with acute renal failure," (in eng), *Crit Care,* vol. 12, no. 3, p. R74, 2008.

[16] M. L. Moritz and J. C. Ayus, "Maintenance Intravenous Fluids in Acutely Ill Patients," (in eng), *N Engl J Med,* vol. 373, no. 14, pp. 1350-60, Oct 2015.

[17] R. Zarychanski *et al.*, "Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis," (in eng), *Jama,* vol. 309, no. 7, pp. 678-88, Feb 20 2013.

[18] N. M. Yunos, R. Bellomo, C. Hegarty, D. Story, L. Ho, and M. Bailey, "Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults," (in eng), *Jama,* vol. 308, no. 15, pp. 1566-72, Oct 17 2012.

[19] P. Young *et al.*, "Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial," (in eng), *Jama,* vol. 314, no. 16, pp. 1701-10, Oct 27 2015.

[20] P. Asfar *et al.*, "High versus low blood-pressure target in patients with septic shock," (in eng), *N Engl J Med,* vol. 370, no. 17, pp. 1583-93, Apr 24 2014.

[21] J. O. Friedrich, N. Adhikari, M. S. Herridge, and J. Beyene, "Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death," (in eng), *Ann Intern Med,* vol. 142, no. 7, pp. 510-24, Apr 5 2005.

[22] N. Lameire, Van Biesen,W., Vanholder,R., "Clinical approach to the patient with acute kidney injury: diagnosis and differential diagnosis," *Oxford Textbook of Clinical Nephrology-4th edition,* vol. 1; chapter 222, pp. 1888-1896, 2015.

[23] K. M. Ho and B. M. Power, "Benefits and risks of furosemide in acute kidney injury," (in eng), *Anaesthesia,* vol. 65, no. 3, pp. 283-93, Mar 2010.

[24] S. M. Bagshaw, R. T. N. Gibney, P. Kruger, I. Hassan, F. A. McAlister, and R. Bellomo, "The effect of low-dose furosemide in critically ill patients with early acute kidney injury: A pilot randomized blinded controlled trial (the SPARK study)," (in eng), *J Crit Care,* vol. 42, pp. 138-146, Jul 12 2017.

[25] R. Bellomo *et al.*, "Acute kidney injury in sepsis," (in eng), *Intensive Care Med,* vol. 43, no. 6, pp. 816-828, Jun 2017.

[26] J. R. Prowle, "Sepsis-Associated AKI," (in eng), *Clin J Am Soc Nephrol,* vol. 13, no. 2, pp. 339-342, Feb 7 2018.

[27] E. Rivers *et al.*, "Early goal-directed therapy in the treatment of severe sepsis and septic shock," (in eng), *N Engl J Med,* vol. 345, no. 19, pp. 1368-77, Nov 08 2001.

[28] P. R. Mouncey *et al.*, "Trial of early, goal-directed resuscitation for septic shock," (in eng), *N Engl J Med,* vol. 372, no. 14, pp. 1301-11, Apr 02 2015.

[29] D. M. Yealy *et al.*, "A randomized trial of protocol-based care for early septic shock," (in eng), *N Engl J Med,* vol. 370, no. 18, pp. 1683-93, May 1 2014.

[30] S. L. Peake *et al.*, "Goal-directed resuscitation for patients with early septic shock," (in eng), *N Engl J Med,* vol. 371, no. 16, pp. 1496-506, Oct 16 2014.
[31] J. R. Prowle, "Fluid resuscitation in septic shock: too much, too little or just right?," (in eng), *Crit Care,* vol. 16, no. 3, p. 436; author reply 436, 2012.
[32] E. A. Hoste *et al.*, "Four phases of intravenous fluid therapy: a conceptual model," (in eng), *Br J Anaesth,* vol. 113, no. 5, pp. 740-7, Nov 2014.
[33] R. P. Dellinger, "The Surviving Sepsis Campaign: 2013 and beyond," (in eng), *Chin Med J (Engl),* vol. 126, no. 10, pp. 1803-5, 2013.
[34] R. P. Dellinger, "The Surviving Sepsis Campaign: Where have we been and where are we going?," (in eng), *Cleve Clin J Med,* vol. 82, no. 4, pp. 237-44, Apr 2015.
[35] A. Joerres, Harper,D., Oppert,M., "Electrolyte and acid-base disorders," *Oxford Textbook of Clinical Nephrology-4th edition,* vol. 1, no. Chapter 230, pp. 1955-1963, 2015.
[36] P. A. McCullough *et al.*, "Acute and chronic cardiovascular effects of hyperkalemia: new insights into prevention and clinical management," (in eng), *Rev Cardiovasc Med,* vol. 15, no. 1, pp. 11-23, 2014.
[37] G. M. McMahon, M. L. Mendu, F. K. Gibbons, and K. B. Christopher, "Association between hyperkalemia at critical care initiation and mortality," (in eng), *Intensive Care Med,* vol. 38, no. 11, pp. 1834-42, Nov 2012.
[38] J. R. Montford and S. Linas, "How Dangerous Is Hyperkalemia?," (in eng), *J Am Soc Nephrol,* vol. 28, no. 11, pp. 3155-3165, Nov 2017.
[39] C. P. Kovesdy, "Management of Hyperkalemia: An Update for the Internist," (in eng), *Am J Med,* vol. 128, no. 12, pp. 1281-7, Dec 2015.
[40] P. Rossignol *et al.*, "Emergency management of severe hyperkalemia: Guideline for best practice and opportunities for the future," (in eng), *Pharmacol Res,* vol. 113, no. Pt A, pp. 585-591, Nov 2016.
[41] Z. Harel, S. Harel, P. S. Shah, R. Wald, J. Perl, and C. M. Bell, "Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review," (in eng), *Am J Med,* vol. 126, no. 3, pp. 264.e9-24, Mar 2013.
[42] J. A. Kraut and N. E. Madias, "Lactic Acidosis: Current Treatments and Future Directions," (in eng), *Am J Kidney Dis,* vol. 68, no. 3, pp. 473-82, Sep 2016.
[43] T. Charron, F. Bernard, Y. Skrobik, N. Simoneau, N. Gagnon, and M. Leblanc, "Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia," (in eng), *Intensive Care Med,* vol. 29, no. 8, pp. 1273-8, Aug 2003.
[44] S. Y. Jung *et al.*, "Phosphate is a potential biomarker of disease severity and predicts adverse outcomes in acute kidney injury patients undergoing continuous renal replacement therapy," (in eng), *PLoS One,* vol. 13, no. 2, p. e0191290, 2018.
[45] R. Claure-Del Granado and J. Bouchard, "Acid-base and electrolyte abnormalities during renal support for acute kidney injury: recognition and management," (in eng), *Blood Purif,* vol. 34, no. 2, pp. 186-93, 2012.
[46] G. S. Markowitz and M. A. Perazella, "Acute phosphate nephropathy," (in eng), *Kidney Int,* vol. 76, no. 10, pp. 1027-34, Nov 2009.
[47] N. Lameire, R. Vanholder, W. Van Biesen, and D. Benoit, "Acute kidney injury in critically ill cancer patients: an update," (in eng), *Crit Care,* vol. 20, no. 1, p. 209, 2016.
[48] A. M. Buchleitner, M. Martinez-Alonso, M. Hernandez, I. Sola, and D. Mauricio, "Perioperative glycaemic control for diabetic patients undergoing surgery," (in eng), *Cochrane Database Syst Rev,* no. 9, p. Cd007315, Sep 12 2012.
[49] V. Brocklebank, K. M. Wood, and D. Kavanagh, "Thrombotic Microangiopathy and the Kidney," (in eng), *Clin J Am Soc Nephrol,* vol. 13, no. 2, pp. 300-317, Feb 7 2018.
[50] A. Joerres, Harper,D., Oppert, M., "Coagulation disturbances," *Oxford Textbook of Clinical Nephrology-4th edition,* vol. 1, chapter 231, pp. 1964-1965, 2015.
[51] M. Heung and L. Yessayan, "Renal Replacement Therapy in Acute Kidney Injury: Controversies and Consensus," (in eng), *Crit Care Clin,* vol. 33, no. 2, pp. 365-378, Apr 2017.
[52] D. M. Nash, S. Przech, R. Wald, and D. O'Reilly, "Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit," (in eng), *J Crit Care,* vol. 41, pp. 138-144, May 09 2017.
[53] P. M. Palevsky, "Renal replacement therapy in acute kidney injury," (in eng), *Adv Chronic Kidney Dis,* vol. 20, no. 1, pp. 76-84, Jan 2013.
[54] M. M. Nair D, Golper TA., "Hybrid Dialysis Techniques in the Intensive Care Unit," in *Critical Care Nephrology*, vol. 1, B. R. Ronco C, Kellum JA, Ricci Z., Ed. Philadelphia: Elsevier, 2017, pp. 966-972.
[55] J. Vanmassenhove, Lameire N, Van Biesen W, Vanholder R., "Outcomes of Intermittent Hemodialysis in Critically Ill patients with Acute Kidney Injury," in *Critical Care Nephrology*, vol. 1, B. R. Ronco C, Kellum JA, Ricci Z., Ed. Philadelphia: Elsevier, 2017, pp. 960-965.
[56] R. Bellomo *et al.*, "Intensity of continuous renal-replacement therapy in critically ill patients," (in eng), *N Engl J Med,* vol. 361, no. 17, pp. 1627-38, Oct 22 2009.
[57] P. M. Palevsky *et al.*, "Intensity of renal support in critically ill patients with acute kidney injury," (in eng), *N Engl J Med,* vol. 359, no. 1, pp. 7-20, Jul 03 2008.
[58] M. E. Malhotra R, Mehta RL, "Starting and Stopping Renal Replacement Therapy in the Critically Ill," in *Critical Care Nephrology* vol. 1, Bellomo. R. Ronco C, Kellum JA, Ricci Z., Ed. Philadelphia: Elsevier, 2017, pp. 873-878
[59] E. A. Burdmann and R. Chakravarthi, "Peritoneal dialysis in acute kidney injury: lessons learned and applied," (in eng), *Semin Dial,* vol. 24, no. 2, pp. 149-56, Mar-Apr 2011.
[60] D. P. Gabriel, J. T. Caramori, L. C. Martin, P. Barretti, and A. L. Balbi, "Continuous peritoneal dialysis compared with daily hemodialysis in patients with acute kidney injury," (in eng), *Perit Dial Int,* vol. 29 Suppl 2, pp. S62-71, Feb 2009.
[61] J. George, S. Varma, S. Kumar, J. Thomas, S. Gopi, and R. Pisharody, "Comparing continuous venovenous hemodiafiltration and peritoneal dialysis in critically ill patients with acute kidney injury: a pilot study," (in eng), *Perit Dial Int,* vol. 31, no. 4, pp. 422-9, Jul-Aug 2011.
[62] D. Ponce and A. Balbi, "Acute kidney injury: risk factors and management challenges in developing countries," (in eng), *Int J Nephrol Renovasc Dis,* vol. 9, pp. 193-200, 2016.
[63] D. Ponce, M. N. Berbel, J. M. Abrao, C. R. Goes, and A. L. Balbi, "A randomized clinical trial of high volume peritoneal dialysis versus extended daily hemodialysis for acute kidney

injury patients," (in Eng), *Int Urol Nephrol,* vol. 45, no. 3, pp. 869-78, Jun 2013.

[64] J. G. Callegari *et al.*, "Peritoneal dialysis for acute kidney injury in sub-Saharan Africa: challenges faced and lessons learned at Kilimanjaro Christian Medical Centre," (in eng), *Kidney Int,* vol. 81, no. 4, pp. 331-3, Feb 2012.

[65] J. Vanmassenhove, R. Vanholder, W. Van Biesen, and N. Lameire, "Haste makes waste-Should current guideline recommendations for initiation of renal replacement therapy for acute kidney injury be changed?," (in eng), *Semin Dial,* vol. 31, no. 3, pp. 204-208, May 2018.

[66] A. Zarbock *et al.*, "Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial," (in eng), *Jama,* vol. 315, no. 20, pp. 2190-9, May 24-31 2016.

[67] S. Gaudry *et al.*, "Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit," (in eng), *N Engl J Med,* vol. 375, no. 2, pp. 122-33, Jul 14 2016.

[68] N. Lameire and J. Vanmassenhove, "Timing of Dialysis in Sepsis and Acute Respiratory Distress Syndrome," (in eng), *Am J Respir Crit Care Med,* Feb 2 2018.

[69] E. M. Borthwick, C. J. Hill, K. S. Rabindranath, A. P. Maxwell, D. F. McAuley, and B. Blackwood, "High-volume haemofiltration for sepsis in adults," (in eng), *Cochrane Database Syst Rev,* vol. 1, p. Cd008075, Jan 31 2017.