Continuous RRT is the preferred modality among many clinicians to achieve specific clinical goals for AKI management

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Overview

The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines have recognized that there is a need to improve outcomes for patients with acute kidney injury (AKI) worldwide,[1] due to the association of AKI with high morbidity and mortality.[1–17]

This document:

- Details the burden of severe AKI requiring renal replacement therapy (RRT) for patients.
- Describes the different RRT modalities available for the treatment of critically ill patients with AKI.
- Discusses the evidence-based clinical guidelines recommending continuous RRT as the preferred RRT modality for patients with AKI who are hemodynamically unstable or require precise fluid management.
- Considers the solutions available for use with continuous RRT modalities.
- Provides an overview of Baxter's commitment to improving patient outcomes for the most critically ill.

AKI in the acute setting

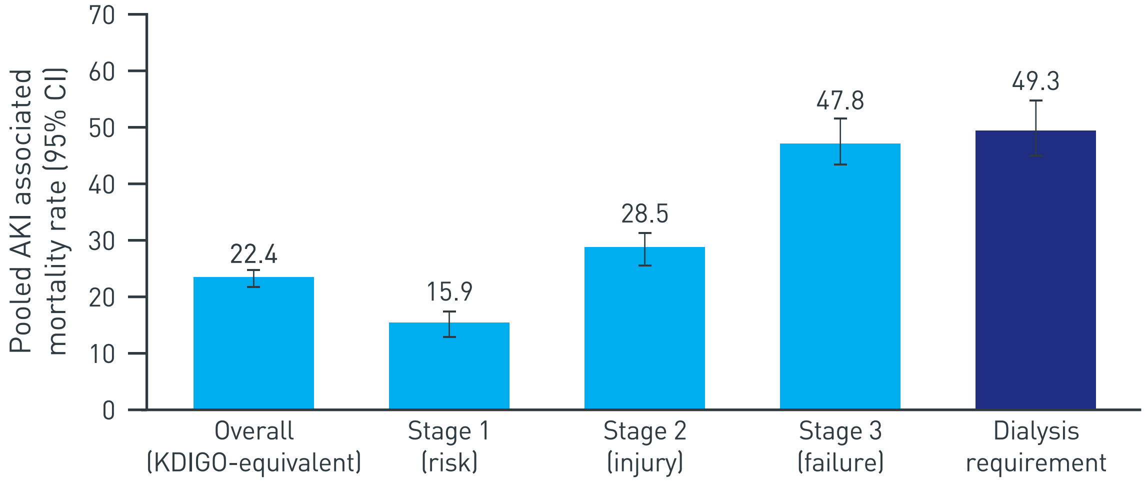
AKI is defined as an abrupt decrease in kidney function that occurs over a period of 7 days or less, encompassing both direct injury to the kidney as well as acute impairment of function.[1]

AKI is a global problem and is common among critically ill patients. The reported incidence of AKI in the intensive care unit (ICU) ranges from 0.5% to 78.7%,[18–22] and up to ~25% of these patients may require RRT.[23–26]

The coronavirus disease 2019 (COVID-19) pandemic has impacted the landscape of AKI globally, as kidney dysfunction is common among patients with severe COVID-19.[27] AKI is reported to affect ~45% of patients with COVID-19 requiring ICU care, with one in five patients with COVID-19 admitted to the ICU receiving RRT.[27]

AKI confers a significant burden for patients, and is associated with an increased risk of morbidity,[2–12] progression to chronic kidney disease (CKD), including end-stage renal disease,[16,17] and short- and long-term mortality[13–16] compared with no AKI (figure 1). The risk of morbidity and mortality increases with increasing AKI severity,[5–10] with patients with AKI requiring RRT at the greatest risk of reduced survival and the development of life-threatening consequences.[6,13,28,29]

FIGURE 1. POOLED IN-HOSPITAL AKI-ASSOCIATED MORTALITY[28,29]



	Overall (KDIGO-equivalent)	Stage 1 (risk)	Stage 2 (injury)	Stage 3 (failure)	Dialysis requirement
No. studies	106	26	25	25	30
No. patients with AKI	341,061	8,226	42,354	42,354	5,979

AKI, acute kidney injury; CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes.

What does this mean? Of all patients with AKI, those requiring RRT are among the most severely ill, with the greatest risk of in-hospital mortality.[28,29]

Figure adapted from: Susantitaphong P, *et al*. Correction. *Clin J Am Soc Nephrol*. 2014; 9:1148. Copyright © 2014, with permission from the American Society of Nephrology. Available at: https://cjasn.asnjournals.org/content/9/6/1148.

RRT modalities for the treatment of critically ill patients with AKI

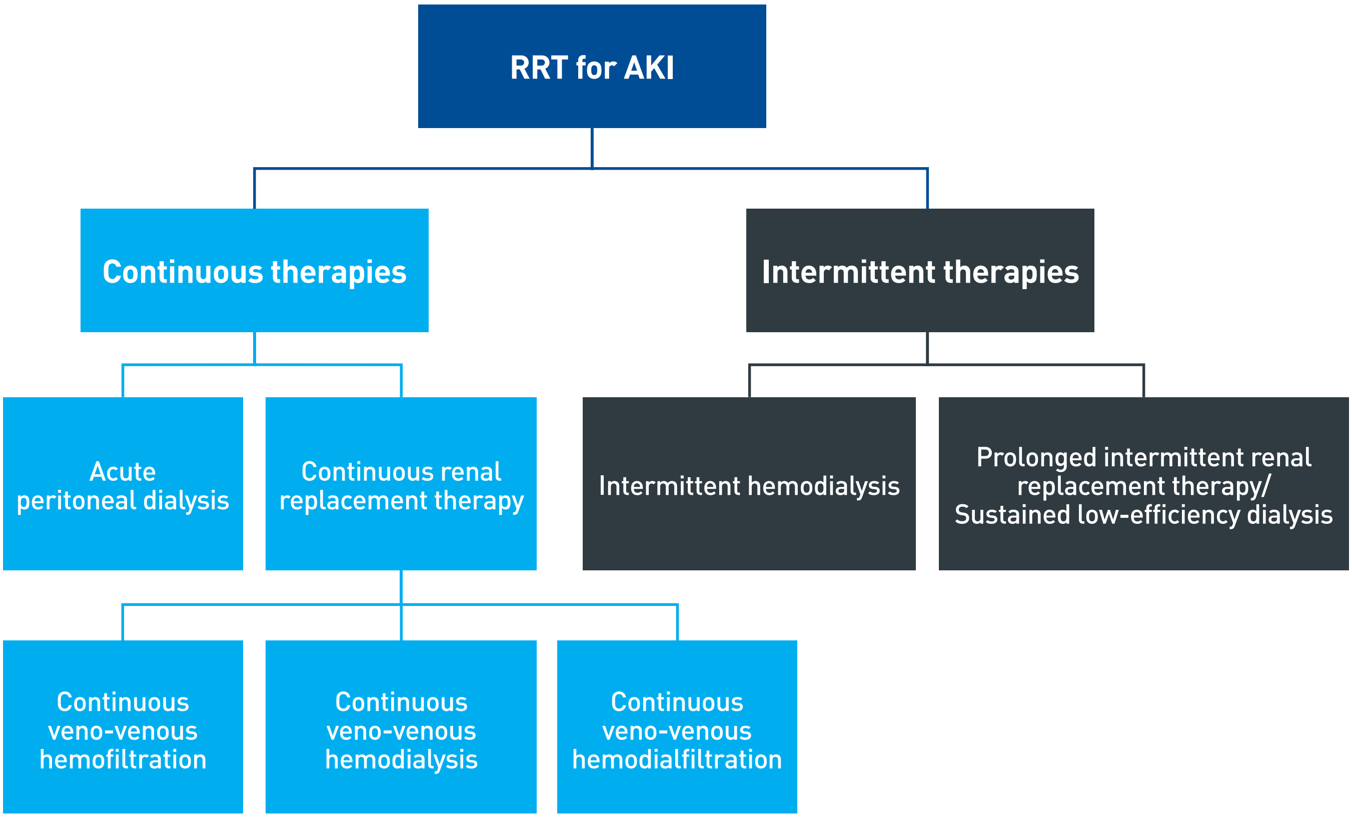
RRT represents a cornerstone of treatment for patients with severe AKI.[30] The KDIGO clinical practice guidelines suggest initiation of "*RRT emergently when life-threatening changes in fluid, electrolyte, and acid–base balance exist (not graded).*"[1,a]

The goals of RRT for critically ill patients with AKI include maintaining fluid, electrolyte, acid–base, and solute balance, supporting renal recovery, preventing additional kidney damage, and allowing other supportive interventions to proceed without complication or limitation.[1] RRT can achieve these goals by mimicking the non-endocrine function of the kidney.[30,31]

A number of RRT modalities are available for the management of patients with severe AKI, which can be classified as continuous or intermittent (figure 2).[1,31–34] Different RRT modalities can be utilized during the course of AKI to meet the patient's evolving clinical needs.[1] The KDIGO clinical practice guidelines suggest to "*use continuous and intermittent RRT as complementary therapies in AKI patients (not graded).*"[1,a]

Continuous RRT defines any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and aimed at being applied continuously for 24 hours per day.[35] The duration and frequency that intermittent RRT modalities are applied for varies depending on the patient's catabolic, metabolic, and hemodynamic state.[36]

FIGURE 2. RRT MODALITIES AVAILABLE FOR TREATMENT OF SEVERE AKI[1,31,32,34]



AKI, acute kidney injury; RRT, renal replacement therapy.

[a] Suggestions that are "not graded" are based on consensus of the KDIGO group, and are given when the topic does not allow adequate application of evidence.[1]

Continuous RRT

Continuous RRT modalities utilize different clearance mechanisms for fluid and solute removal, including ultrafiltration, adsorption, diffusion, and convection (table 1).[1,37,b]

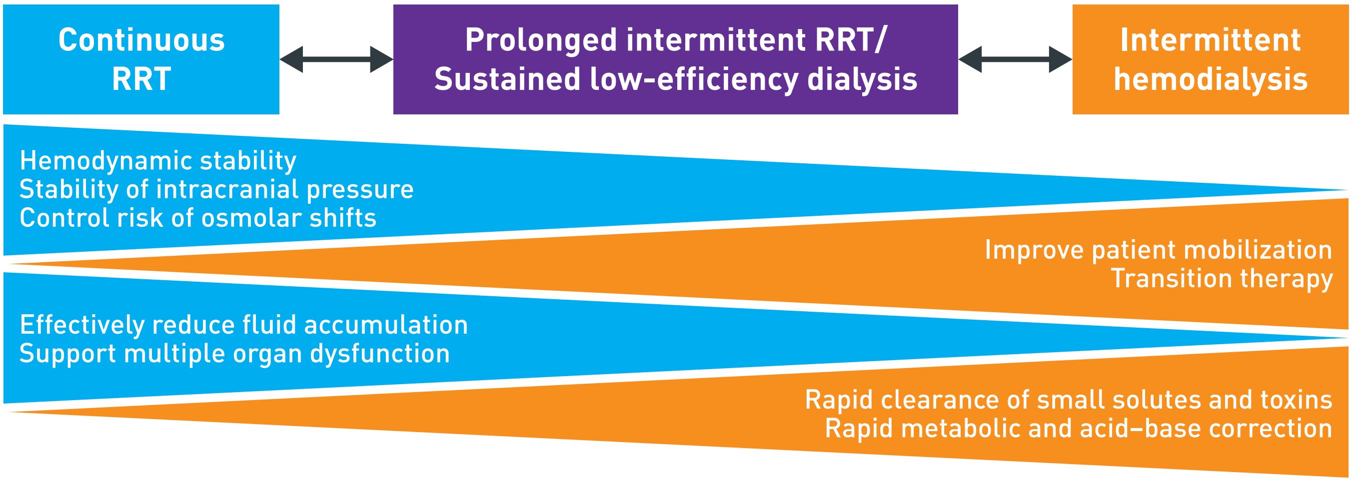
TABLE 1. MECHANISMS OF FLUID AND SOLUTE REMOVAL UTILIZED BY CONTINUOUS RRT MODALITIES[1,37]

Continuous RRT modality	Mechanism of removal			
	Ultrafiltration	Adsorption[b]	Diffusion	Convection
Continuous veno-venous hemodiafiltration (CVVHDF)	✓	✓	✓	✓
Continuous veno-venous hemodialysis (CVVHD)	✓	✓	✓	
Continuous veno-venous hemofiltration (CVVH)	✓	✓		✓

CVVH, Continuous veno-venous hemofiltration; CVVHD, Continuous veno-venous hemodialysis; CVVHDF, Continuous veno-venous hemodiafiltration; RRT, renal replacement therapy.

As continuous veno-venous hemodiafiltration (CVVHDF) combines the convective solute removal of continuous veno-venous hemofiltration (CVVH) with the diffusive solute removal of continuous veno-venous hemodialysis (CVVHD),[1,36] the continuous RRT modality can theoretically facilitate effective removal of small and middle molecules, via diffusion and convection, respectively.[37–40]

FIGURE 3. THEORETICAL ADVANTAGES OF CONTINUOUS RRT AND INTERMITTENT RRT MODALITIES PROPOSED BY THE 17TH ACUTE DISEASE QUALITY INITIATIVE (ADQI) WORKGROUP[41,42]



RRT, renal replacement therapy.

What does this mean? The theoretical advantages of each RRT modality enable the different modalities to be utilized during the course of AKI to meet the patient's evolving clinical needs.[1]

[b] Solutes may be removed by adsorption during continuous RRT depending on the type of membrane used in the extracorporeal circuit.[37]

Continuous RRT for the treatment of critically ill patients with AKI

Given the burden of AKI, expert nephrologists have published objective, evidence-based clinical guidelines to improve the care and outcomes of patients with kidney disease worldwide.[1,43,44] These clinical guidelines provide suggestions and recommendations for the clinical scenarios in which continuous RRT may be the preferred RRT modality for critically ill patients with AKI.[1,42,45,46]

Continuous RRT is the preferred modality for precise fluid management

"Continuous types of RRT are recommended in situations where shifts in fluid balance and metabolic fluctuations are poorly tolerated"[42]

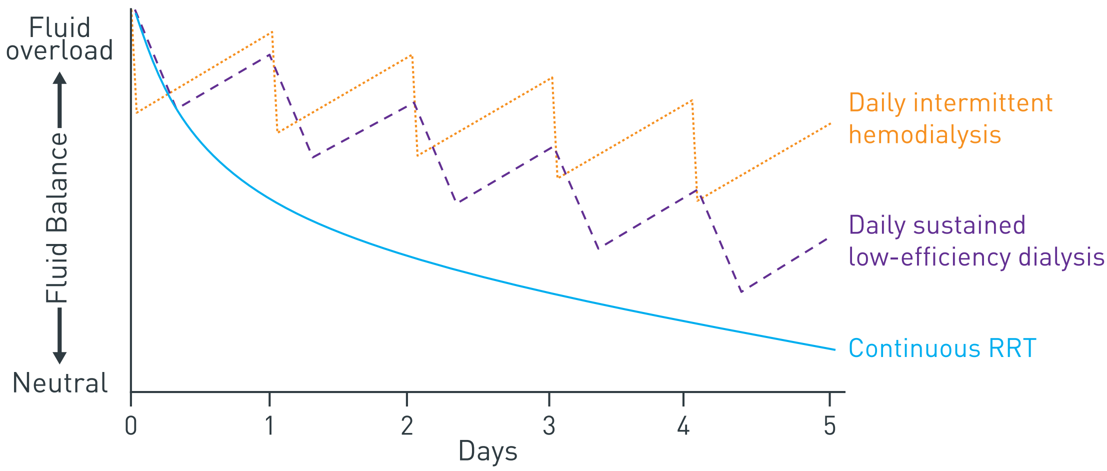
Patient Selection and Timing of Continuous Renal Replacement Therapy, 17th ADQI Workgroup, 2016.

Fluid overload is common early after ICU admission,[47] and is associated with an increased risk of mortality and major adverse kidney events (a composite outcome consisting of all-cause mortality, RRT dependence, or an inability to recover more than 50% of baseline estimated glomerular filtration rate if not on RRT) up to 90 days following hospital discharge ($MAKE_{90}$).[26,48] Continuous RRT has been shown to reduce fluid accumulation in an effective and timely manner (figure 4),[49,50] providing the flexibility to adjust fluid removal intensity at any time according to changes in the patient's clinical condition.[1] Continuous RRT modalities allow the integration of machine fluid balance with dynamic changes in patient fluid balance by adding and adjusting machine fluid balance to net patient inputs and outputs, allowing precise management of fluid balance.[51]

A number of studies have investigated the relationship between fluid overload and patient outcomes among critically ill patients.[26,48] Evidence from the Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) study indicates that there is an exponential relationship between maximum fluid accumulation and the predicted probability of death in critically ill patients admitted to the ICU; every 1% increase of maximum fluid overload was associated with an odds ratio (OR) of 1.075 for hospital mortality (95% CI 1.055–1.095, unadjusted model).[26]

Woodward CW, *et al*. conducted a single-center, retrospective cohort study in the United States (US) (2014–2016) investigating fluid accumulation among 481 critically ill patients with AKI requiring continuous RRT.[48] Of the 481 patients, 411 were found to have fluid accumulation of ≥0.[48] A sensitivity analysis of this patient subgroup found that each 1% increase in fluid accumulation was significantly associated with a 2.1% increase in adjusted odds of $MAKE_{90}$ ($P = 0.041$).[48] A multivariable analysis also found that fluid accumulation of >10% was associated with an 82% increased odds of hospital mortality (adjusted OR 1.82, $P = 0.004$), and 2.5 fewer ventilator-free days, compared with fluid accumulation ≤10% ($P = 0.044$).[48.]

FIGURE 4. FLUID BALANCE OVER TIME IN PATIENTS RECEIVING CONTINUOUS RRT VS. INTERMITTENT RRT MODALITIES, SUCH AS DAILY SUSTAINED LOW-EFFICIENCY DIALYSIS AND DAILY INTERMITTENT HEMODIALYSIS

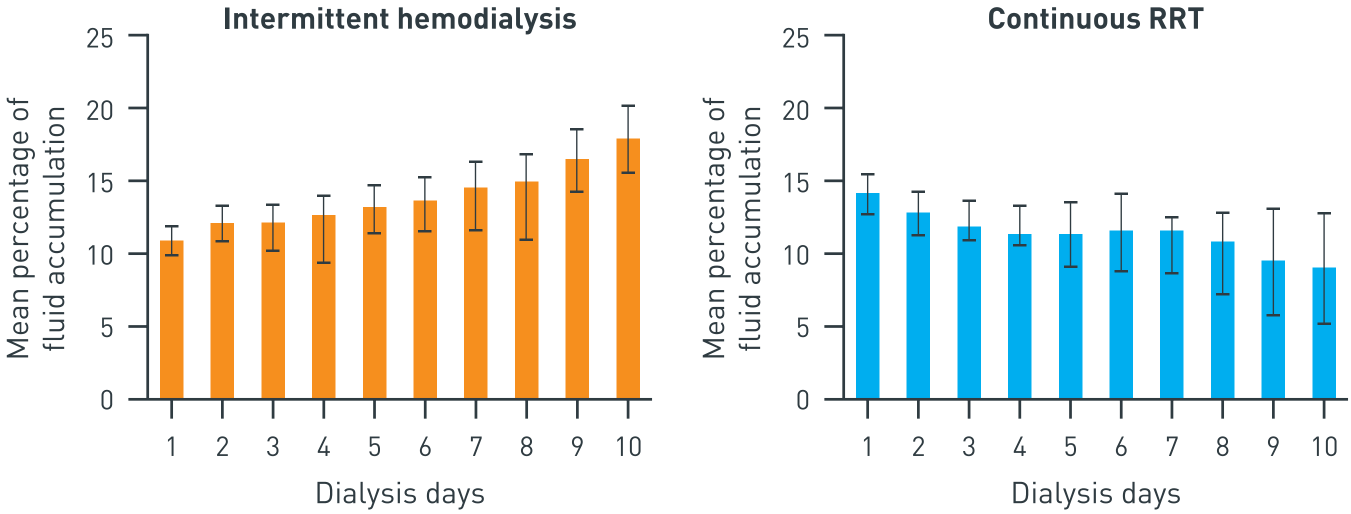


RRT, renal replacement therapy.

A randomized controlled trial (RCT) conducted by Augustine JJ, *et al*. at a single institution in the United States (US) (1995–1999) investigated cumulative fluid balance over 3 days in critically ill patients with AKI treated with continuous RRT (CVVHD performed continuously during the 72-hour period) vs. intermittent RRT (intermittent hemodialysis [IHD]).[49,c] Median cumulative total fluid balances over 3 days were −4,005 mL (range, −13,533 to +6,745 mL) for the CVVHD group and +1,539 mL (range, −5,510 to +9,152 mL) for the IHD group ($P < 0.001$).[49]

The prospective, multicenter, observational PICARD study, conducted between 1999 and 2001, investigated fluid accumulation in 610 patients with AKI treated with continuous RRT vs. patients with AKI treated with IHD at five centers in North America.[50] Though no statistical comparisons were reported, continuous RRT with CVVHD was more likely to reduce the percentage of fluid accumulation compared with intermittent RRT (IHD) (figure 5).[50]

FIGURE 5. FLUID ACCUMULATION OVER TIME IN PATIENTS WITH AKI TREATED WITH IHD VS. CONTINUOUS RRT[50]



RRT, renal replacement therapy.

What does this mean? Existing medical evidence suggests that continuous RRT may be able to provide better control of fluid management compared with other intermittent RRT modalities.[1,49,50]

Continuous RRT is the preferred modality for patients with AKI or cardiac surgery-associated acute kidney injury (CSA-AKI) who are hemodynamically unstable

"We suggest using CRRT rather than standard intermittent RRT for hemodynamically unstable patients (grade 2B)"[1,d]

KDIGO Clinical Practice Guideline for Acute Kidney Injury, 2012.

"We recommend the use of continuous therapies in [CSA-AKI] patients with hemodynamic instability and in situations in which shifts in fluid balance are poorly tolerated (grade 1B)"[46,e]

Cardiac and Vascular Surgery–Associated Acute Kidney Injury: The 20th International Consensus Conference of the ADQI Group, 2018.

[c] The first day of dialysis was classified as Day 1.[49]
[d] Statements graded "Level 2" are classified as suggestions; statements graded "B" are supported by moderate-quality evidence.[1]
[e] Statements graded "Level 1" are classified as recommendations; statements graded "B" are supported by high-quality evidence.[46]
Figure adapted from: Bouchard J, *et al. Kidney Int*. 2009; 76:422–427.

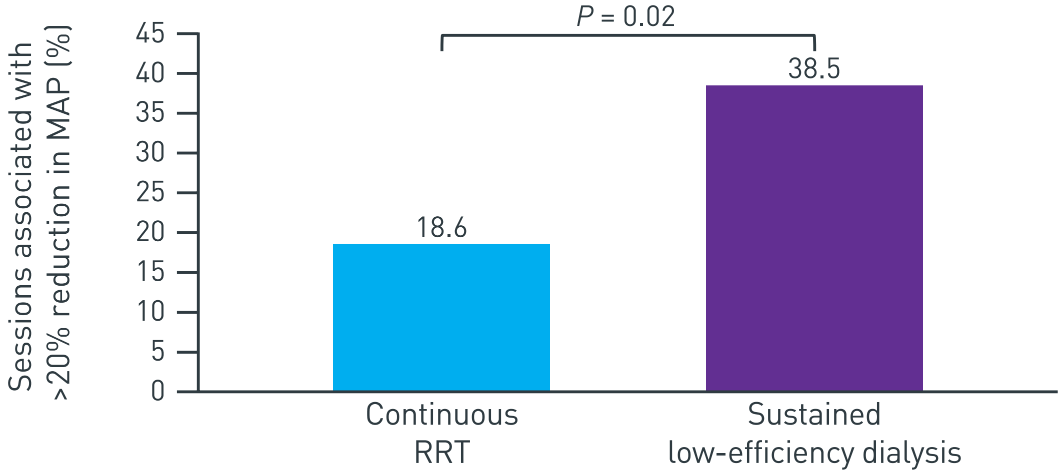
Hemodynamic instability is common among critically ill patients with AKI receiving RRT (~36–70% of patients),[52,53] and may be associated with an increased risk of mortality and AKI progression.[54,55] Continuous RRT removes fluid in a slow and continuous manner, in theory reducing the likelihood of fluctuations in intravascular fluid volume, thereby helping to maintain hemodynamic stability.[1,51,56]

Continuous RRT may have a better hemodynamic profile compared with intermittent therapies, including IHD and sustained low-efficiency dialysis (SLED).[49,57] An RCT conducted by Augustine JJ, *et al*. at a single institution in the US (1995–1999) investigated hemodynamic stability in critically ill patients with AKI (n = 80) treated with intermittent vs. continuous RRT modalities, and found that the use of IHD was associated with reduced mean arterial pressure (MAP) compared with continuous RRT (CVVHD) during the first dialysis day (difference in MAP in mmHg, −0.8 vs. +0.6, respectively, $P = 0.04$).[49]

A prospective cohort study conducted by Fieghen HE, *et al*. investigated hemodynamic instability among patients with AKI from four critical care units within a single university-affiliated medical center (N = 77) being treated predominantly with IHD (n = 34), continuous RRT (n = 30), or SLED (n = 13).[58] The use of SLED was associated with an increased frequency of RRT sessions that resulted in a >20% reduction in MAP compared with continuous RRT (38.5% vs. 18.6%, $P = 0.02$).[58] Hemodynamic instability, defined by a composite of MAP decline of >20% or the need to escalate vasopressors, occurred in 56.4% of SLED sessions and 50.0% of continuous RRT sessions ($P = 0.51$), with an adjusted OR of hemodynamic instability for SLED vs. continuous RRT of 1.20, 95% CI 0.58–2.47.[58] Fieghen HE, *et al*. concluded that SLED provides comparable hemodynamic control to continuous RRT (figure 6).[58]

A German RCT conducted by John S, *et al*. over a 2-year period assessed the influence of CVVH vs. IHD on systemic hemodynamics and splanchnic regional perfusion in adult patients with septic shock and acute renal failure (n = 30), and found that the use of intermittent RRT (IHD) was associated with increased heart rate and reduced systolic blood pressure compared with continuous RRT (CVVH).[57]

FIGURE 6. SESSIONS ASSOCIATED WITH HEMODYNAMIC INSTABILITY AMONG PATIENTS WITH AKI BEING TREATED WITH CONTINUOUS RRT VS. SLED[58,f]



What does this mean? Existing medical evidence suggests that continuous RRT may be better able to maintain hemodynamic stability while removing fluid compared with intermittent therapies, such as IHD and SLED.[49,58,59]

[f] Hemodynamic instability was defined by a composite of MAP decline of >20% or the need to escalate use of vasopressors.[58]
AKI, acute kidney injury; MAP, mean arterial pressure; RRT, renal replacement therapy.
Figure adapted from: Fieghen HE, *et al. BMC Nephrol*. 2010; 11:32.

Continuous RRT may be the preferred modality for infection control when managing patients with COVID-19 AKI

"CRRT machines (if available) are preferred over IHD machines in the setting of biocontainment/isolation"[45]

U.S. Centers for Disease Control and Prevention, Considerations for Providing Hemodialysis to Patients with Suspected or Confirmed COVID-19 in Acute Care Settings, 2020.

Given the infectious nature of COVID-19, the safety of healthcare providers is an important consideration when treating the disease and its complications, including AKI.[45] As such, the U.S. Centers for Disease Control and Prevention recommend the use of personal protective equipment and the appropriate disposal of dialysis effluent from patients with suspected or confirmed COVID-19, as per standard facility protocols, and that acute RRT should be performed in an isolated room, if available, with the door closed.[60] Additionally, the American Society of Nephrology recommends using continuous RRT rather than intermittent modalities when treating patients with AKI and suspected or confirmed COVID-19.[45]

What does this mean? The continuous nature of continuous RRT reduces close contact between healthcare providers and AKI patients with suspected or confirmed COVID-19, potentially reducing the risk of healthcare providers contracting COVID-19.[45]

Solutions for continuous RRT

The composition of dialysate and replacement solutions used with continuous RRT modalities can differ in concentrations of potassium, magnesium, calcium, bicarbonate, and dextrose.[51] These variable concentrations allow tailoring of dialysate and replacement fluids to meet the needs of the individual patient; adding bicarbonate as a buffer helps correct metabolic acidosis, and adding sodium helps achieve a desired serum sodium concentration for maintenance of high serum osmolarity in patients with cerebral edema.[1,51] In addition to continuous RRT solutions tailored on-site, prescribing physicians may also use pre-made, commercially available dialysate and replacement solutions designed to meet their patient's needs.[51]

As replacement fluids are infused directly into the blood, they must be sterile.[1] For patients in whom acute RRT is indicated, continuous RRT can be applied without the substantial water requirements of intermittent therapies,[61,62] and can be useful in settings with disrupted or limited water supply.[62]

Baxter's support for patients in critical care

At Baxter, we recognize the complexity of the challenges clinicians face when caring for the most critically ill patients and providing the right therapy for the right patient.

Baxter is dedicated to partnering with healthcare providers to help personalize and optimize patient centered care. Baxter's Integrated Care Solutions portfolio expands treatment possibilities for patients with AKI, helping clinicians to provide quality care. The **PrisMax** system has been developed to meet the evolving needs of critical care by enabling delivery of the continuous RRT therapies of both today and tomorrow.

Baxter's experienced clinical team provides tailored training and shares best practices to enable healthcare professionals to maximize their critical care program.

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Summary

- AKI is a global problem associated with poor patient outcomes.
- RRT represents a major component of AKI management, particularly in severe cases, with different modalities to address the patient's evolving clinical needs during the course of disease.
- Continuous RRT is the preferred RRT modality for patients with AKI who are hemodynamically unstable or require precise fluid management.
- Solutions for continuous RRT can be tailored to meet patient's specific needs healthcare providers to help personalize and optimize patient-centered care.
- Baxter is dedicated to partnering with healthcare providers to help personalize and optimize patient-centered care.

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