# Continuous Kidney Replacement Therapies: Core Curriculum 2025

*J. Pedro Teixeira, Swapnil Hiremath, Abdulghani Omar Kabli, Oleksa G. Rewa, and Edward G. Clark*

Critically ill patients that require kidney replacement therapy (KRT) are among the most ill and complex patients routinely encountered in the intensive care unit (ICU). Continuous KRT (CKRT) is used across many ICUs as the therapy of choice for hemodynamically unstable patients with kidney failure. Though existing trials have not shown superior survival or kidney recovery with CKRT relative to intermittent KRT, CKRT has largely become the standard of care in developed nations for the treatment of acute kidney injury (AKI) in patients with shock, acute brain injury, acute liver failure, and other forms of critical illness. As health care systems provide an ever-widening scope of organ-support therapies to increasingly complicated ICU patients, the use of CKRT is likely to expand. In this Core Curriculum, we review the physicochemical principles of CKRT, provide a comprehensive yet practical review of when and how to prescribe CKRT, and summarize seminal trials that serve as the foundations for our approaches to timing of initiation, dosing, vascular access, and anticoagulation for CKRT. We conclude by briefly highlighting a variety of essential, yet often underappreciated, components of the provision of high-value multidisciplinary care to patients receiving CKRT, including drug dosing, nutrition, physical rehabilitation, and CKRT quality assurance programs.

*Complete author and article information provided at end of article.*

*Am J Kidney Dis. 85(6):767-786. Published online March 9, 2025.*

*doi: 10.1053/j.ajkd.2024.09.015*





*The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.*

## Introduction

Since its introduction in the late 1970s, continuous kidney replacement therapy (CKRT) has evolved to become a mainstay in the care of critically ill patients with kidney failure. CKRT is used across many intensive care units (ICUs) internationally as the kidney replacement therapy (KRT) of choice for patients with hemodynamic instability.

Most broadly, CKRT encompasses blood purification techniques intended to run for 24 hours or longer without interruption. For any daily ultrafiltration volume, continuous treatment allows for a lower ultrafiltration rate than is possible with intermittent KRT. This, in conjunction with a slower rate of solute clearance, may make CKRT hemodynamically better tolerated than intermittent KRT modalities. Despite these theoretical advantages, clinical trials have not demonstrated survival benefits or improvements in kidney function recovery with CKRT compared with intermittent KRT modalities in patients with acute kidney injury (AKI).

Since the publication of "Continuous Dialysis Therapies: Core Curriculum 2016," greater consensus has been achieved regarding several important aspects of the application of CKRT. Nonetheless, wide practice variation persists regarding the specific modalities employed and many other aspects of the CKRT prescription. The relatively recent development of quality metrics related to CKRT presents a path toward standardization and improved care.

In this update to *AJKD*'s Core Curriculum in Nephrology series, we focus on key concepts and their supporting medical literature in order to guide nephrologists in the safe and maximally beneficial provision of CKRT for critically ill patients.

## Advantages and Disadvantages of CKRT

***Case 1:*** *A 28-year-old woman is admitted to the ICU after a motor vehicle collision with prolonged extrication. She is diagnosed with traumatic brain injury with intraparenchymal hemorrhage and multiple fractures with rhabdomyolysis with an initial creatine kinase (CK) level of 40,000 U/L. After 48 hours, despite aggressive intravenous fluids followed by intravenous (IV) furosemide at 1 mg/kg, she is severely oliguric, with 110 mL of urine produced in the prior 24 hours. She has required several boluses of 23.4% sodium chloride to control intracranial hypertension with a goal serum sodium of >150 mEq/L. On examination, her blood pressure is 142/91 mm Hg without vasopressor support, and her weight is 60 kg. She is unresponsive and receiving mechanical ventilation with an intracranial pressure (ICP) monitor in place and 1-2+ generalized edema. Her laboratory results now include sodium, 154 mEq/L; potassium, 6.1 mEq/L; creatinine, 3.3 mg/dL (0.9 mg/dL on admission); and phosphate, 8.2 mg/dL, with*

*CK >100,000 U/L (above limit of detection). The chest X-ray is clear. Repeat head computed tomography (CT) shows a stable large left frontal hemorrhage with surrounding cerebral edema and persistent 4-mm midline shift. Her most recent ICP is 21 mm Hg.*

**Question 1: Which of the following is the most appropriate next step?**

(a) Manage hyperkalemia medically with insulin and albuterol.

(b) Prescribe intermittent hemodialysis without anticoagulation.

(c) Initiate CKRT with prefilter heparin anticoagulation and a continuous infusion of 3% sodium chloride to generate an effective CKRT bath of 152 mEq/L.

(d) Initiate CKRT with no anticoagulation and a continuous infusion of 3% sodium chloride to generate an effective CKRT bath of 152 mEq/L.

*For the answer to this question, see the following text.*

Randomized controlled trials (RCTs) comparing CKRT to intermittent KRT modalities (ie, intermittent hemodialysis [IHD] or various forms of prolonged intermittent kidney replacement therapy [PIKRT]) are challenging to undertake because CKRT is already viewed by many clinicians to be the standard of care for critically ill patients. Although theoretically less likely to provoke or exacerbate hemodynamic instability than intermittent KRT modalities, studies have reported mixed results: some have found less hypotension or decreased vasopressor requirements with CKRT while others have not. Furthermore, although observational data suggest CKRT is better for kidney recovery, prior trials (despite their limitations) have reported equivalent mortality and recovery of kidney function. Thus, CKRT, IHD and PIKRT are all reasonable options for critically ill patients with AKI who can tolerate them hemodynamically. Nonetheless, practical considerations may favor or disfavor the use of CKRT in selected clinical scenarios (Table 1).

CKRT should be the preferred KRT modality for patients with intracranial hypertension. Because urea is distributed throughout the body water but only slowly crosses the blood-brain barrier, overly rapid clearance of urea from the circulation using intermittent forms of KRT can promote the shift of plasma water into the brain. This "reverse urea effect" can precipitate or exacerbate intracranial hypertension with disastrous neurologic consequences. Severe hepatic failure is associated with cerebral edema and intracranial hypertension, so CKRT should similarly be favored for such patients.

Beyond its slower rate of solute clearance, the relatively low ultrafiltration rates required for equivalent volume removal with CKRT versus intermittent KRT modalities make CKRT a particularly useful option when high obligate fluid intake necessitates large ultrafiltration volumes on an ongoing basis (eg, anuric patients requiring total parenteral nutrition).

Although the major advantages of CKRT relate to more-gradual ultrafiltration and solute removal than is possible with intermittent KRT modalities, for the same reasons it is ill-suited for very rapidly correcting fluid, electrolyte, or acid-base abnormalities. For example, intermittent KRT modalities should be preferred for most intoxications or when extreme metabolic derangements necessitate very rapid correction (see the section "Dose of Solute Clearance With CKRT").

Regarding Case 1, though all KRT modalities can potentially exacerbate intracranial hypertension, this patient with diuretic-refractory oliguria and severe rhabdomyolysis is very unlikely to be successfully managed without KRT, so (a) is incorrect. Though IHD, due to higher blood flow rate ($Q_b$), can often be performed without anticoagulation, IHD is the *most likely* KRT modality to exacerbate intracranial hypertension and should be avoided in this scenario, which makes (b) incorrect. Moreover, because some commercially available IHD machines can only generate a dialysate sodium up to 145 mEq/L, maintaining therapeutic hypernatremia > 150 mEq/L can be difficult. Due to the lower dialysate flow rate ($Q_d$) and/or replacement fluid rate ($Q_r$) used, maintaining an effective sodium bath of >150 mEq/L is feasible with CKRT and hypertonic saline infusion (see the section "Adjusting Plasma Composition").

When using heparin for CKRT anticoagulation, infusion in the prefilter position may improve filter life by increasing the intrafilter concentration of heparin. However, regardless of where it is infused, heparin is heavily protein-bound and is *not* removed by any KRT modality. Therefore, unless used with protamine reversal, prefilter heparin produces systemic anticoagulation and is contraindicated in this patient, and therefore (c) is incorrect.

Instead, either attempting CKRT without anticoagulation—as in (d), the correct answer—or using regional citrate anticoagulation (RCA), which has no systemic anticoagulant effect, would be reasonable options in this case.

## Additional Readings


- Clark WR, Villa G, Neri M, Ronco C. Advances in machine technology. *Contrib Nephrol.* 2018;194:80-89. doi:10.1159/000485604 ★ESSENTIAL READING
- Davenport A. Continuous renal replacement therapies in patients with acute neurological injury. *Semin Dial.* 2009;22:165-168. doi:10.1111/j.1525-139X.2008.00548.x
- Douvris A, Zeid K, Hiremath S, et al. Mechanisms for hemodynamic instability related to renal replacement therapy: a narrative review. *Intensive Care Med.* 2019;45:1333-1346. doi:10.1007/s00134-019-05707-w ★ESSENTIAL READING
- Schneider AG, Bellomo R, Bagshaw SM, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med.* 2013;39(6):987-997. doi:10.1007/s00134-013-2864-5

**Table 1.** Possible Indications for CKRT and Potential Advantages and Disadvantages of CKRT (Relative to IHD or PIKRT) in Critically Ill Patients With AKI

| Classic Indications for KRT in the Setting of Hemodynamic Instability | CKRT-specific Indications: Need for KRT in the Setting of Specific Critical Care Scenarios | Advantages of CKRT | Disadvantages of CKRT |
|---|---|---|---|
| • Severe hyperkalemia<br>• Severe metabolic acidosis<br>• Diuretic-resistant volume overload<br>• Life-threatening or severe complications of uremia (eg, bleeding in the setting of uremic platelet dysfunction, pericarditis)<br>• Poisoning with dialyzable toxins (eg, toxic alcohols, salicylates, lithium)[a]<br>• Persistent oliguria or anuria | • Intracranial hypertension or conditions associated with elevated ICP or requiring maintenance of therapeutic hypernatremia (eg, acute liver failure, acute brain injury)<br>• Gradual correction of severe dysnatremia (eg, serum [$Na^+$] < 120 mEq/L or >165 mEq/L)<br>• Cardiopulmonary failure requiring ECMO or other mechanical circulatory support<br>• Organ support in patients with advanced heart or liver disease unable to tolerate IHD, especially when used as a bridge to transplantation or other destination therapy<br>• Conditions requiring continuous solute removal due to high cell turnover or cell lysis (eg, rhabdomyolysis or tumor lysis syndrome) | • Less hypotension<br>• Less effect on ICP in at-risk patients (eg, acute brain injury; acute liver failure)<br>• Superior volume control<br>• Superior solute control (ie, higher total daily or weekly dose)<br>• Usually permits nutrition without restriction in protein, phosphate, or potassium<br>• Less hemodialysis nurse support[b] | • Decreased (ie, slower) instantaneous clearance<br>• Increased need for circuit anticoagulation due to extended treatment time<br>• Increased risk of hypophosphatemia<br>• Requires catheter placement[c]<br>• Increased risk of immobilization[d]<br>• More ICU nurse support[b]<br>• Increased overall cost |

Adapted with permission from: Teixeira JP, Neyra JA, Tolwani A. Continuous KRT: A Contemporary Review. *Clin J Am Soc Nephrol* 2023; 18: 256-269. Abbreviations: AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ECMO, extracorporeal membrane oxygenation; ICP, intracranial pressure; ICU, intensive care unit; IHD, intermittent hemodialysis; KRT, kidney replacement therapy; PIKRT, intermittent kidney replacement therapy; [$Na^+$], sodium concentration.
[a]IHD, given its faster clearance, is generally preferred over CKRT in the treatment of poisonings, but high-dose CKRT can be considered in patients with severe hemodynamic instability.
[b]Relative amounts of dialysis versus ICU nurse support will depend on local staffing models.
[c]Though 1 single-center observational study suggests using arteriovenous fistulae/grafts for CKRT may be safe and feasible, doing so is not standard of care in most institutions.
[d]Note that CKRT is *not* a contraindication to early mobilization per se as observational data suggest that physical rehabilitation is feasible and safe in patients on CKRT, but many providers perceive CKRT to be a barrier to physical therapy.

## CKRT Principles

Unlike intermittent KRT techniques, CKRT is employed on an ongoing basis to achieve continuous solute and fluid homeostasis. The basic requirements for effective CKRT are the same as for other forms of extracorporeal KRT: (1) a well-functioning vascular access (ie, dual-lumen intravenous hemodialysis catheter); (2) a semipermeable membrane (ie, dialyzer/hemofilter); (3) a blood pump (ie, roller pump); (4) for most CKRT modalities, additional roller pump(s) to circulate dialysate and/or replacement solutions across the membrane or into the circuit; and (5) fluid-balancing and pressure monitoring systems. The various forms of CKRT in common use are primarily defined by their mechanisms of solute clearance.

### Solute Transport and Membrane Characteristics

CKRT can be used to remove solutes via convection, diffusion, or a combination of both. Largely depending on membrane characteristics, adsorption of solutes occurs in all CKRT circuits, resulting in some large-molecule clearance though this is typically limited by saturation of membrane-binding sites within several hours of CKRT initiation. Diffusion, the primary mechanism of solute clearance in IHD, is driven by a difference in solute concentration in plasma water and dialysate across a membrane (dialyzer). Convection (or, more precisely, advection) is the bulk movement of solute within fluid across a membrane (hemofilter) due to a hydrostatic pressure difference (Fig 1).

The primary mechanism for solute removal differentiates techniques and underpins CKRT terminology (Table 2). Continuous venovenous hemofiltration (CVVH) only utilizes convection, continuous venovenous hemodialysis (CVVHD) primarily utilizes diffusion (though some internal filtration and back-filtration occurs), and continuous venovenous hemodiafiltration (CVVHDF) uses both. For all modalities, the extended duration of CKRT allows for gradual solute equilibration. For CVVH, the total effluent flow rate ($Q_{ef}$) is equal to the machine net ultrafiltration rate ($UF_{net}$) plus $Q_r$. (For an explanation of machine vs patient $UF_{net}$, see the section "Achieving Fluid Balance.") For CVVHD, $Q_{ef}$ is equal to $UF_{net}$ plus the $Q_d$. For CVVHDF, $Q_{ef}$ is equal to $UF_{net}$ plus $Q_r$ plus $Q_d$.

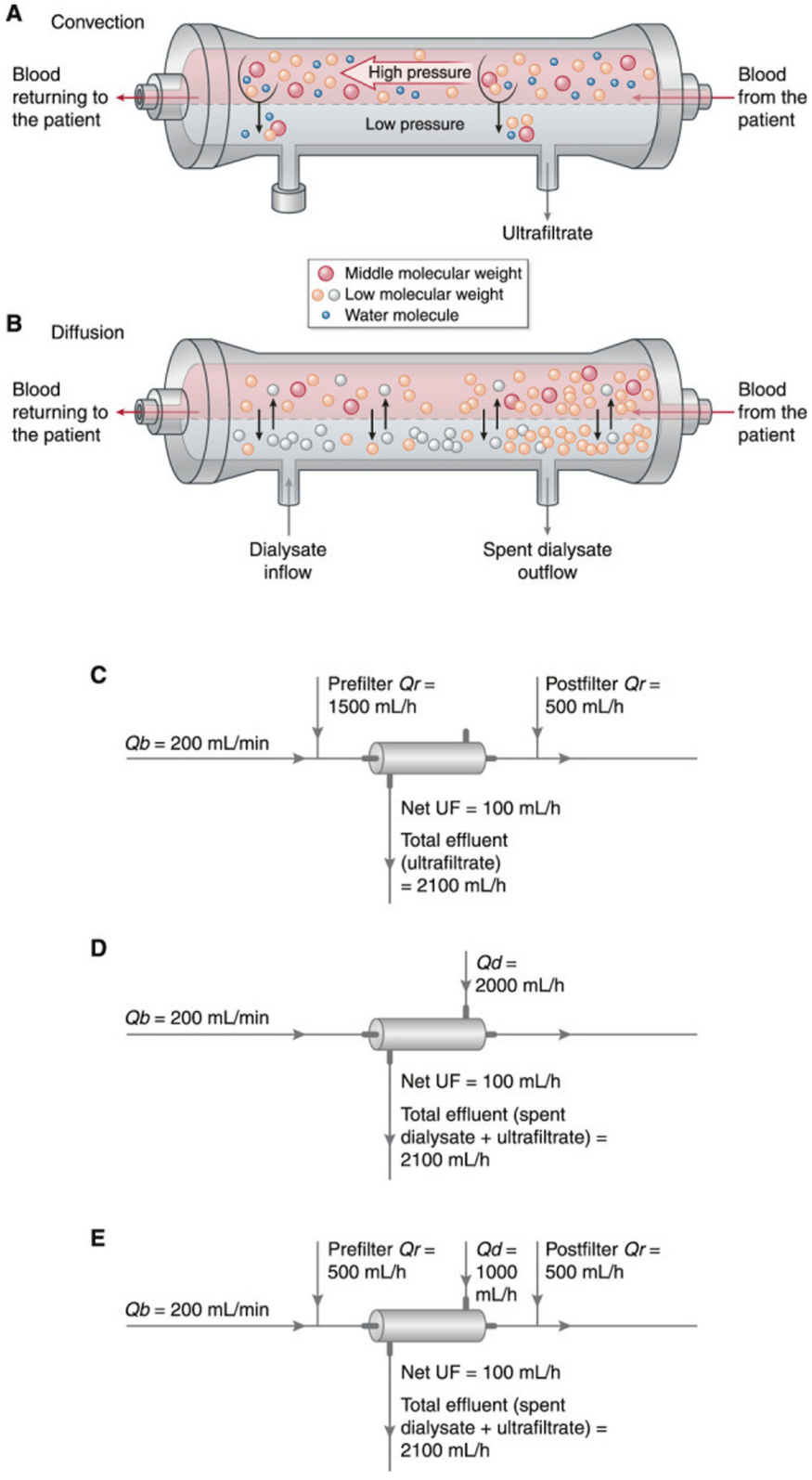



**Figure 1.** CKRT modalities, circuits, and pressure monitoring. (A) In hemofiltration, solute clearance occurs primarily by convection.[a] In convection, solutes are transported across the hemofilter membrane along with plasma water as a result of a hydrostatic pressure (ie, transmembrane pressure) generated on the blood side of the membrane. Solutes cleared by convection include urea and other small molecules along with larger "middle molecules." (B) In hemodialysis, solute clearance occurs primarily by diffusion,[b] which is driven by a concentration gradient across the semipermeable membrane. Small solutes in high concentration in the blood diffuse across the membrane into the dialysate, which contains either little (eg, potassium) or none (eg, urea) of the solutes being cleared.

F

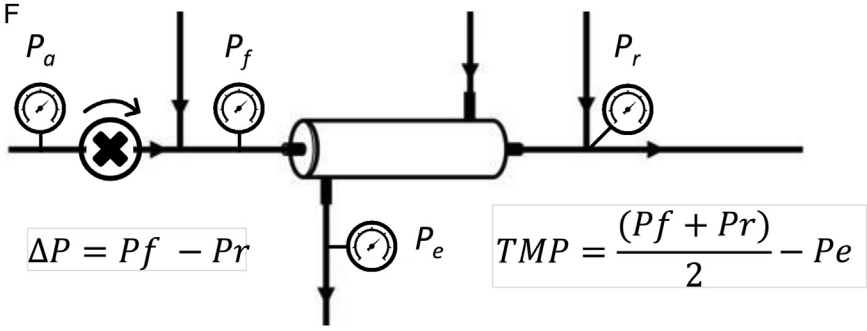



**Figure 1.** (*continued*).

The filter clearance of small solutes (eg, potassium, urea) can be estimated by $Q_{ef}$ once membrane permeability is constant (ie, the adsorptive limit of the membrane is reached). Filter clearance of a solute is equal to the product of $Q_{ef}$ and the sieving coefficient ($S$) for the solute. $S$ is the ratio of solute concentration in the effluent ($C_{ef}$) to the

**Figure 2 (Con'd).** Small solutes in higher concentration in the dialysate (eg, bicarbonate) diffuse into the blood. Dialysate runs across the dialysis membrane countercurrent to the direction of blood flow to maintain a concentration gradient for removal of small solutes along the entire length of the semipermeable membrane. Modern hemodialyzers are virtually all "high-flux" dialyzers, which clear substances larger than historical low-flux dialyzers. However, unlike hemofiltration, hemodialysis does not effectively clear larger middle molecules. Ultrafiltration can be performed with hemodialysis by applying a transmembrane pressure across the membrane, but, in contrast to the high volume of ultrafiltration used to achieve significant solute clearance in hemofiltration, the volumes of ultrafiltration performed in hemodialysis are relatively small, contribute little to small solute clearance, and are instead used only to achieve net volume removal. (C) In CVVH, a high volume of ultrafiltrate is generated and is replaced with an equal or (if net volume removal is desired) a somewhat smaller amount of physiologic crystalloid solution to effect net solute removal. The physiologic solution may be infused before the hemofilter (prefilter replacement fluid), into the return line (postfilter replacement fluid), or both. The machine net ultrafiltration rate (UF) is equal to the difference between the effluent rate and the replacement fluid rate(s) ($Q_r$), and it is adjusted to achieve net volume removal as desired. A typical CVVH prescription is shown, which, for a 70 kg patient, would provide a total dose of 30 mL/kg/h and a net ultrafiltration rate of 100 mL/h. To maintain efficient solute clearance in CVVH, blood flow rate ($Q_b$) should be kept approximately 5 to 6 times higher than the replacement fluid rates. (D) In CVVHD, dialysate is driven through the dialyzer across the membrane from the blood flow in a direction countercurrent to blood flow. In most settings, the dialysate solution used in CVVHD is very similar or identical to the replacement fluid used in CVVH. In contrast with CVVH, ultrafiltration in CVVHD makes only a minor contribution to solute removal but is performed primarily for the purposes of volume management, with ultrafiltrate generated at a rate equal to the desired rate of fluid removal. The effluent consists of both the spent dialysate and ultrafiltrate, and the net ultrafiltration rate is equal to the difference between the total effluent flow rate and the dialysate flow rate ($Q_d$). A typical CVVHD prescription is shown, which, for a 70 kg patient, again provides a total dose of 30 mL/kg/h and a net ultrafiltration rate of 100 mL/h. To maintain efficient solute clearance in CVVHD, blood flow rate should be kept approximately 2.5 times higher than the dialysate flow rate. (E) CVVHDF combines a high volume of ultrafiltration coupled with replacement fluid (to achieve solute clearance by convection) with dialysate perfused across the membrane countercurrent to blood flow (to achieve solute clearance by diffusion). As in CVVH, ultrafiltrate volume in excess of the desired rate of fluid removal is replaced with a physiologic crystalloid solution that may be infused before the hemofilter (prefilter replacement fluid), into the return line (postfilter replacement fluid), or both. The effluent consists of both the spent dialysate and ultrafiltrate with the net ultrafiltration rate equal to the difference between the total effluent flow rate and the sum of dialysate and total replacement fluid flow rates. A typical CVVHD prescription is shown, which, for a 70 kg patient, again provides a total dose of 30 mL/kg/h and a net ultrafiltration rate of 100 mL/h. (F) CKRT devices typically have manometers to measure pressure throughout the extracorporeal circuit, including within the access line before the blood pump ($P_a$), between the pump and hemofilter ($P_f$, or filter pressure), in the return line ($P_r$), and in the effluent line ($P_e$). The pressure within the hemofilter is not readily measured but can be estimated by averaging the pressure entering and exiting the hemofilter (ie, [$P_f$ + $P_r$]/2). Dysfunction of the vascular access often manifests with extreme (very negative and very positive, respectively) $P_a$ and $P_r$. Hemofilter clogging, in which the blood path remains patent but the membrane pores are clogged by protein adsorption, results in elevated TMP without significant change in pressure drop across the hemofilter ($\Delta P$). With hemofilter clotting, the blood path and the membrane pores become obstructed by clotted blood and $\Delta P$ and TMP increase simultaneously. [a]Though we retain the use of the term convection used classically in the nephrology literature to describe solute clearance by hemofiltration, the transport of a substance by bulk motion of a fluid is technically *advection* rather than convection. [b]Though small solute clearance with hemodialysis occurs primarily via diffusion, larger solute clearance occurs mostly from the internal filtration and back-filtration that takes place during hemodialysis. Abbreviations: CKRT, continuous kidney replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; TMP, transmembrane pressure; UF, ultrafiltration. Panels A-E reproduced with permission of the copyright holder (Wolters Kluwer Health) from: Teixeira JP, Neyra JA, Tolwani A. Continuous KRT: A Contemporary Review. *Clin J Am Soc Nephrol* 2023; 18(2): 256-269. doi: 10.2215/CJN.04350422. Panel F adapted with permission from Verma S, Palevsky PM. Prescribing Continuous Kidney Replacement Therapy in Acute Kidney Injury: A Narrative Review. *Kidney Med*. 2021;3(5):827-836. doi: 10.1016/j.xkme.2021.05.006

**Table 2.** Transport Mechanisms, Typical Operational Parameters, and Example Prescriptions of the 4 CKRT Modalities

| Parameters | CVVH | CVVHD | CVVHDF | SCUF |
|---|---|---|---|---|
| Primary solute transport mechanism | Convection[a] | Diffusion | Diffusion + convection[a] | Convection[a] |
| Blood flow rate ($Q_b$), mL/min | 100-300 | 100-300 | 100-300 | 100-200 |
| Dialysate flow rate ($Q_d$), mL/h | 0 | 1,000-3,000 | 1,000-2,000 | 0 |
| Replacement fluid rate ($Q_r$), mL/h | 1,000-3,000 | 0 | 1,000-2,000 | 0 |
| Net ultrafiltration rate, ($UF_{net}$), mL/h[b] | 0-300 | 0-300 | 0-300 | 50-300 |
| Total ultrafiltration rate ($UF_{total}$), mL/h | 1,000-3,300 | 0-300 | 1,000-2,300 | 50-300 |
| Components of $UF_{total}$ | $Q_r$+ $UF_{net}$ | $UF_{net}$ | $Q_r$+ $UF_{net}$ | $UF_{net}$ |
| Total effluent rate ($Q_{ef}$) | 1,000-3,300 | 1,000-3,300 | 1,000-3,300 | 50-300 |
| Components of $Q_{ef}$ | $Q_r$+ $UF_{net}$ | $Q_d$+ $UF_{net}$ | $Q_r$+ $Q_d$ + $UF_{net}$ | $UF_{net}$ |

| Modality | Examples of typical prescriptions for a patient weighing 70kg and with hourly net fluid intake of 50 mL/h |
|---|---|
| CVVH | $Q_b$ 200 mL/min, $Q_{r,pre}$ 1,200 mL/h, $Q_{r,post}$ 500 mL/h, $UF_{net}$ = 50 mL/h, $UF_{total}$ = $Q_{ef}$ = 1,750 mL/h (25 mL/kg/min) |
| CVVHD | $Q_b$ 200 mL/min, $Q_d$ 1,700 mL/h, $UF_{net}$ = 50 mL/h, $UF_{total}$ = 50 mL/h, $Q_{ef}$ = 1,750 mL/h (25 mL/kg/min) |
| CVVHDF | $Q_b$ 200 mL/min, $Q_{r,pre}$ 400 mL/h, $Q_d$ 900 mL/h, $Q_{r,post}$ 400 mL/h, $UF_{net}$ = 50 mL/h, $UF_{total}$ = 850 mL/h, $Q_{ef}$ = 1,750 mL/h (25 mL/kg/min) |
| SCUF | $Q_b$ 150 mL/min, $UF_{net}$ = 100 mL/h, $UF_{total}$ = $Q_{ef}$ = 100 mL/h (1.4 mL/kg/min) |

These ranges are typical operating parameters but do not represent maximal achievable values in any case. Adapted from: Macedo E, Mehta RL. Continuous Dialysis Therapies: Core Curriculum 2016. *Am J Kidney Dis*. 2016;68(4):645-657. doi: 10.1053/j.ajkd.2016.03.427. Abbreviations: CKRT, continuous kidney replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; $Q_d$, rate of dialysate fluid instilled into filter countercurrent to flow of blood; $Q_r$, rate of fluid instilled prefilter ($Q_{r,pre}$) or postfilter ($Q_{r,post}$) to replace ultrafiltrate volume; SCUF, slow continuous ultrafiltration; $UF_{total}$, rate of plasma water removed from circulating blood into the effluent, driven by the machine settings to include the quantity of pre- and postdilution replacement fluids ($Q_r$) plus the desired net fluid removal ($UF_{net}$).
[a]Strictly speaking, solute clearance during hemofiltration is via advection rather than convection.
[b]$UF_{net}$ rate in this table refers to machine net ultrafiltration (rather than patient net ultrafiltration) and is referred to as "patient fluid removal" on some CKRT devices; as such, in the examples provided, the CVVH, CVVHD, and CVVHDF prescriptions would achieve patient net even fluid balance, whereas the SCUF prescription would achieve patient net negative balance of 50 mL/h. Though listed here to be complete, the solute clearance (ie, $Q_{ef}$) provided by SCUF is considered clinically negligible.

solute concentration in plasma ($C_p$). This is determined according to the reflection coefficient ($\sigma$) of the membrane ($S = 1 - \sigma$). A solute with an $S$ of 1 passes freely through filters whereas a solute with an $S$ of 0 does not pass at all. For middle-sized molecules, clearance depends of the membrane characteristics and the ultrafiltration volume (convective clearance). For solutes that undergo adsorption, clearance from blood can exceed filter clearance even when $S$ is low, resulting in a mismatch between clearance from blood and filter clearance.

Modern CKRT devices utilize hollow-fiber high-flux hemofilters which can be used for hemodialysis or hemofiltration. High-flux hemofilters are now standard in developed countries for both IHD and CKRT. High-flux refers to the larger size cutoff for solutes removed via hemodialysis, with internal filtration/back-filtration particularly contributing to large solute clearance. For high-flux hemofilters, this size cutoff is substantially higher (up to ~10,000 Daltons) than for the low-flux hemofilters historically used for IHD (~1,000 Daltons). The use of high-flux hemofilters in hemofiltration allows for removal of solutes up to ~40,000 Daltons in size. Importantly, these size cutoffs likely overestimate in vivo cutoffs because effective pore size decreases within hours of use due to adsorption of plasma proteins onto hemofilters. In contrast to flux, efficiency describes the maximal small-molecule clearance that a given hemofilter can inherently achieve, which is largely a reflection of the membrane surface area and its permeability to solute.

Because clearance in CKRT is typically limited by $Q_d$ and/or $Q_r$, hemofilters used in CKRT are typically lower efficiency than those used for IHD due to smaller surface area (eg, ~1 $m^2$ rather than ~2 $m^2$ for IHD, as typical adult sizes). Membrane charge somewhat effects solute clearance, particularly for middle-sized molecules removed by convection, and the tendency for solute adsorption onto membranes. In general, middle- and large-sized molecules are less likely to adsorb onto uncharged membranes (eg, membranes composed of polyarylethersulfone [PAES]) compared with negatively charged membranes, such as AN69 membranes composed of acrylonitrile and sodium methallyl sulfonate copolymer). Consequently, uncharged membranes are likely less prone to *clog* than negatively charged membranes. In contrast to clotted hemofilters, clogging of hemofilters means the membrane pores have been occluded (Fig 1). Though clotting and clogging often occur together, conceptually a clogged but unclotted hemofilter will not allow movement of solute or fluid across the membrane's pores but still permits passage of blood through the filter.

Notably, the middle-sized solutes potentially removed or adsorbed by hemofiltration include a variety of inflammatory mediators (eg, interleukin-1 [IL-1], IL-6, IL-8, and tumor necrosis factor-α). Convective removal of these cytokines with high-volume hemofiltration (HVHF) has

been investigated as a treatment for patients with septic AKI or septic shock, after cardiac surgery, and in other critical illnesses. Although HVHF has been shown in some studies to reduce vasopressor requirements, RCTs of HVHF have failed to demonstrate any benefit in meaningful outcomes such as mortality or kidney recovery. Because trials have not demonstrated superiority of CVVH, CVVHD, or CVVHDF or of any specific CKRT machine, ultimately the choice of CKRT modality or device in many centers is predicated more on local equipment availability and practice patterns than on the theoretical differences between these modes of clearance or on specific machine features.

## CKRT Modalities

### Continuous Venovenous Hemofiltration

CVVH uses only convection: an ultrafiltrate ($U_f$) is generated by a transmembrane pressure (TMP) gradient across the hemofilter membrane. The process of convection is represented by the equations,

$$U_f = K_f \times \text{TMP}$$

$$\text{TMP} = \left(P_b - P_{uf}\right) - \pi$$

where $K_f$ is the coefficient of hydraulic permeability, $P_b$ represents the hydrostatic pressure in the blood, $P_{uf}$ represents the hydrostatic pressure in the ultrafiltrate, and $\pi$ represents plasma oncotic pressure. The convective clearance ($C_x$) of a solute is estimated by the following equations:

$$C_x = Q_{uf} \times S$$

$$S = C_{uf}/C_p$$

where $S$ is the sieving coefficient, $C_p$ is the plasma solute concentration, and $C_{uf}$ represents the ultrafiltrate solute concentration.

CVVH requires the use of replacement fluid to replace either all or most of the ultrafiltrate, with replacement of less than all the ultrafiltrate resulting in net ultrafiltration (ie, net volume removal). The replacement fluid composition can vary and can be infused pre- and/or post-hemofilter. In CVVH, dialysate is not used. Typically, CVVH employs a relatively high rate of ultrafiltration (eg, 20-25 mL/kg/h), with solute cleared at the same rate. However, because ultrafiltration alone would not lead to any change in plasma solute concentration and the high rate of ultrafiltration would rapidly result in volume depletion, replacement fluid is given. Administration of replacement fluid results in a lowering via dilution of the plasma water solute concentration of removed solutes that are not present in the replacement solution (eg, urea).

### Continuous Venovenous Hemodialysis

CVVHD removes small solutes primarily by diffusion. Dialysate fluid is pumped countercurrent to the direction of blood flow. Ultrafiltration—apart from some degree of internal filtration/back-filtration—occurs only at the rate for which net fluid removal (ie, net ultrafiltration) is desired. This results in a small amount of small solute removal via convection, though filtration/back-filtration contributes to larger solute clearance. No replacement solution is used with CVVHD.

Solute diffusion ($S_d$) in CVVHD is estimated using the following equation,

$$S_d = \left(C_g/M_t\right) \times D \times T \times A$$

where $C_g$ is the concentration gradient, $M_t$ is membrane thickness, $D$ is the diffusion coefficient of the solute, $T$ is the temperature of the solution, and $A$ is the membrane surface area. $C_g$ is generally impacted by $Q_d$ and $Q_b$. However, because $Q_d$ is much lower than $Q_b$ (typically 8-50 mL/min vs 100-200 mL/min), near-complete saturation of dialysate usually occurs during CVVHD. Consequently, $Q_d$ is the rate-limiting factor for small solute removal, minimally affected by $Q_b$ within the ranges of $Q_d$ and $Q_b$ typically prescribed for CVVHD.

### Continuous Venovenous Hemodiafiltration

CVVHDF is a hybrid of CVVH and CVVHD, removing solutes using both convection and diffusion, using both replacement and dialysate solutions. The ultrafiltration rate determines convective clearance, with the use of replacement fluid producing solute dilution. As with CVVH, the rate of net fluid removal can be increased by increasing the ultrafiltration rate above $Q_r$. As with CVVHD, dialysate is also pumped countercurrent to blood flow across the hemofilter, with $Q_d$ determining diffusive clearance.

### Slow Continuous Ultrafiltration

Slow continuous ultrafiltration (SCUF) is the simplest form of CKRT, consisting of ultrafiltration without fluid replacement. Ultrafiltrate is generated by a hydrostatic pressure difference across the hemofilter. $Q_b$ is typically 100-200 mL/min. Clearance is minimal because the only solute loss is that which is contained in the ultrafiltrate, which is produced at the same rate as the desired net fluid removal and is low relative to the ultrafiltration rate utilized to achieve solute clearance with CVVH. No diffusive clearance occurs because no dialysate fluid is used. SCUF is used to treat isolated fluid overload in patients without any need for solute clearance. Notably, the trials assessing SCUF performed using peripheral venous access in patients with heart failure showed no mortality benefit compared with protocolized diuretic use.

## Fluid Management

With CKRT, plasma composition is adjusted by altering the composition of dialysate and/or replacement fluids while the net ultrafiltration rate is adjusted separately, allowing for precise, simultaneous, and independent management of fluid balance and plasma composition. For example, the

plasma sodium level can be maintained at any targeted level while the fluid balance is kept even, negative, or positive.

### Adjusting Plasma Composition

CKRT allows one to select dialysate and replacement fluid composition to achieve a desired change in plasma composition and to precisely control the rate of correction of electrolyte abnormalities, especially dysnatremias. With some important exceptions, most CKRT solutions provide physiologic or near-physiologic concentrations of most electrolytes (Table 3).

CKRT solutions most commonly vary in their concentrations of potassium, calcium, and bicarbonate. Because the total daily dose of solute clearance provided by CKRT is higher than that provided by thrice weekly or even daily IHD (Table 4), the concentration of potassium in CKRT solutions required to control hyperkalemia is typically not as low as is required in IHD (eg, usually 4 mEq/L is sufficient unless hyperkalemia is severe). Acetate or lactate were historically used as primary buffers in KRT solutions, but modern CKRT solutions are almost exclusively bicarbonate based, with typical bicarbonate concentrations of 22 to 35 mEq/L.

CKRT solutions used with RCA are usually free of calcium, which facilitates lowering the intrafilter calcium concentration. Additionally, these solutions usually have lower concentrations of bicarbonate (typically ~25 mEq/L) than other standard CKRT solutions (usually ~35 mEq/L), to account for the alkali load that citrate represents after being metabolized by the liver. Unlike lactate, which generates an equimolar amount of bicarbonate when metabolized, each citrate molecule is metabolized to 3 bicarbonate molecules. Importantly, although commercially available phosphate-containing CKRT solutions are now available, traditional CKRT solutions are devoid of phosphate.

With IHD, dialysate sodium concentration can be manipulated in a continuous fashion within a limited range (usually 130-145 mEq/L) by altering the dialysate conductivity, but generating effective sodium dialysate concentrations outside this range is impractical due to the comparatively high $Q_d$ used in IHD. In contrast, though the sodium concentrations of premanufactured CKRT solutions are set, the relatively low $Q_d$ and $Q_r$ used in CKRT allow for easier manipulation of the effective sodium concentration, enabling slow and controlled correction of severe hyponatremia or hypernatremia.

When correcting severe hyponatremia, lowering the effective sodium bath can be achieved by diluting the CKRT solutions by adding sterile water to the bag or replacing some CKRT solution with sterile water. Generally, this approach is impractical if commercially available CKRT solutions are used because large volumes of sterile water are not routinely stocked in hospitals due to the safety risk of inadvertent systemic administration, and the addition and removal of fluid from premade sterile bags carries the risk of imprecision or a breach of sterility. Institutions that have pharmacy-prepared CKRT solutions may be better able to customize low-sodium concentration solutions, though such an approach also carries the inherent risk of compounding errors and microbial contamination.

Another approach when using commercially available solutions is to provide an additional infusion of dextrose 5% in water (D5W) either into the CKRT circuit, usually in the postfilter position, or via a separate systemic infusion. In hyponatremic patients, the additional volume of D5W ($V_{D5W}$) in liters per hour to administer to achieve a targeted sodium concentration ($[Na^+]_T$) can be calculated when $Q_{ef}$ is the total effluent flow rate in liters per hour and $[Na^+]_{CKRT}$ is the sodium concentration in the dialysate and/or replacement fluid (in mmol/L):

$$V_{D5W} = \left[Q_{ef} \times \left([Na^+]_{CKRT} - [Na^+]_T\right)\right] \Big/ [Na^+]_T$$

For example, to target a sodium concentration of 125 mmol/L using CKRT with commercially available solutions having a sodium concentration of 140 mmol/L while using 2.5 L/h total effluent rate, $V_{D5W}$ can be calculated as follows:

$$\begin{aligned} V_{D5W} &= (2.5\ \text{L/h} \times (140\ \text{mmol/L} - 125\ \text{mmol/L}))/ \\ &\quad 125\ \text{mmol/L} \\ &= (350\ \text{mmol/h} - 312.5\ \text{mmol/h})/125\ \text{mmol/L} \\ &= 0.3\ \text{L/h} \end{aligned}$$

The additional VD5W is removed via ultrafiltration on an ongoing basis according to the desired net ultrafiltration rate.

When needing CKRT solutions with a high effective sodium concentration to gradually correct severe hypernatremia or to achieve therapeutic hypernatremia, hypertonic saline can either be added to CKRT solutions (usually as 23.4% sodium chloride) or can be infused (usually as 3% sodium chloride) into the CKRT circuit or systemically. For example, for the 60 kg patient described in Case 1, an appropriate total effluent dose of 25 mL/kg/h would be 1,500 mL/h, which, with a sodium concentration of 140 mEq/L in most standard CKRT solutions, would deliver 140 mEq/L × 1.5 L/h = 210 mEq/h of sodium, regardless of modality. A 3% sodium chloride solution could be infused (either within the CKRT circuit, often as the post-filter replacement fluid, or via a separate infusion) at 50 mL/h to provide 513 mEq/L × 0.05 L/h = 25.7 mEq/h of additional sodium. Combined, this would deliver 235.7 mEq/h of sodium in 1.55 L/h, generating an effective sodium bath of (235.7 mEq/h) / (1.55 L/h) = 152 mEq/L.

### Achieving Fluid Balance

As previously outlined, one major practical advantage of CKRT is that it can continuously and gradually remove fluid. CKRT machines utilize either gravimetric or

**Table 3.** Examples of CKRT Solutions Available Worldwide

| | Citrate-free Solutions | | | | | Citrate-containing Solutions | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Components | PrismaSol BGK, B22GK, or BK | PrismaSATE BGK, B22GK, BK, or BzK | Phoxillum BK or B22K | PureFlow B RFP 400-456 | Duosol 4551-4556 | 4% Sodium Citrate | ACD-A | Regiocit | Prismocitrate 10/2 | Prismocitrate 18/0 | Citra-HF Pre |
| $Na^+$, mEq/L | 140 | 140 | 140 | 130 or 140 | 140 or 136 | 408 | 225 | 140 | 136 | 140 | 139.9 |
| $K^+$, mEq/L | 4, 2, or 0 | 4, 2, or 0 | 4 | 4, 3, 2, or 0 | 4, 2, or 0 | — | — | — | — | — | 3 |
| $Ca^{++}$, mEq/L | 0, 2.5, or 3.5 | 0, 2.5, or 3.5 | 0 or 2.5 | 0, 2.5, or 3 | 0 or 3 | — | — | — | — | — | — |
| $Mg^{++}$, mEq/L | 1, 1.2, or 1.5 | 1, 1.2, or 1.5 | 1.5 | 1 or 1.5 | 1 or 1.5 | — | — | — | — | — | 0.5 |
| $HCO_3^-$, mEq/L | 32 or 22 | 32 or 22 | 32 or 22 | 35 or 25 | 35, 32, or 25 | — | — | — | — | — | — |
| Lactate, mEq/L | 3 | 3 or 0 | — | — | — | — | — | — | — | — | — |
| $Cl^-$, mEq/L | 108-120.5 | 108-120.5 | 114.5 or 122 | 108.5-120.5 | 107.5-117 | — | — | 86 | 106 | 86 | 104 |
| Dextrose, mg/dL | 100 or 0 | 110 or 0 | — | 100 | 100 or 0 | — | 2,230 | — | — | — | 90 |
| Trisodium citrate, mmol/L | — | — | — | — | — | 136 | 75 | 18 | 10 | 18 | 13.3 |
| Citric acid, mmol/L | — | — | — | — | — | — | 38 | — | 2 | — | — |

No citrate formulation is currently approved by the US Food and Drug Administration for CKRT anticoagulation, and such use is considered off-label. Both 4% sodium citrate and ACD-A are used as anticoagulants infused into the CKRT circuit in the prefilter position, whereas Regiocit, Prismocitrate solutions, and Citra-HF Pre are dilute citrate solutions formulated in 5 L bags designed for use as alternatives to standard CKRT solutions. In the United States, 4% sodium citrate and ACD-A are generic agents with multiple manufacturers. PrismaSol, PrismaSATE, Phoxillum, and Regiocit are manufactured by Baxter International (Deerfield, IL). PureFlow B solutions are manufactured by NxStage Medical (Lawrence, MA), a subsidiary of Fresenius Medical Care (Bad Homburg, Germany). Duosol solutions are manufactured by B Braun (Bethlehem, PA). PrismaSol is marketed and regulated in the United States as a replacement fluid (ie, as a drug) and may be used as either replacement fluid or dialysate. PrismaSATE, PureFlow B, and Duosol are marketed and regulated as dialysate only (ie, devices rather than drugs) and are only authorized for use as dialysate. Regiocit is only FDA-approved under emergency use authorization (EUA). Prismocitrate solutions (Baxter) and Citra-HF Pre (Nordic Medcom, Espoo, Finland) are only available outside the United States. Table © 2024 Ashita Tolwani, MD and Rajesh Speer, PharmD and is reproduced with permission of the copyright holder. Abbreviations: ACD-A, anticoagulant citrate dextrose solution A; CKRT, continuous kidney replacement therapy.

**Table 4.** Comparison of KRT Modalities by Theoretical Maximal Clearances and Estimated Typical Weekly Doses

| | Maximal Theoretical Clearance (mL/min) | Typical Approximate Total Weekly Dose (ie, Standardized Kt/$V_{urea}$) |
|---|---|---|
| IHD, 3 times/wk | 280 | 2 |
| IHD, 7 times/wk | 280 | 5 |
| PD, 7 times/wk | 16 | 2 |
| CKRT, postfilter CVVH, 25 mL/kg/h | 25 | 7 |
| CKRT, prefilter CVVH, 35 mL/kg/h | 28 | 8 |
| CKRT, postfilter CVVH, 35 mL/kg/h | 35 | 10 |
| CKRT, CVVHD, 35 mL/kg/h | 35 | 10 |
| PIKRT | Variable | Variable |
| Normal kidney | 90-140 | 16 |

For CKRT and IHD, clearance values represent theoretical maximums, assuming hematocrit 30%, body weight 60 kg, total body water 36 L, IHD blood flow rate of 400 mL/min, CKRT blood flow rate of 200 mL/min, sieving coefficient of 1, and dialysate saturation (ie, extraction ratio) of 100%. Estimated Kt/V values for CKRT similarly assume theoretical maximal values, with no downtime, filter efficiency loss, or patient fluid overload. Standardized Kt/V values for IHD assume single-pool Kt/V of 1.3, representing typical goal clearance rather than maximal theoretical achievable dose. For PD, the maximal theoretical clearance assumes rapid cycling prescription with 50% equilibration of dialysate versus plasma (ie, $D/P_{creatinine} = 0.5$) using 2 L of dialysate exchanged every hour, whereas the Kt/V is calculated assuming a 70-kg patient treated with continuous ambulatory PD with dialysate drain volume of 10.2 L/d and complete equilibration between dialysate and plasma water (ie, $D/P_{creatinine} = 1$). Based on data in Diaz-Buxo JA, Loredo JP. Standard Kt/V: comparison of calculation methods. *Artif Organs*. 2006;30(3):178-185. doi:10.1111/j.1525-1594.2006.00204.x; Ghannoum M, Roberts DM, Hoffman RS, et al. A stepwise approach for the management of poisoning with extracorporeal treatments. *Semin Dial*. 2014;27(4):362-370. doi:10.1111/sdi.12228; and Clark WR, Leblanc M, Ricci Z, Ronco C. Quantification and dosing of renal replacement therapy in acute kidney injury: a reappraisal. *Blood Purif*. 2017;44(2):140-155. doi:10.1159/000475457. Abbreviations: CKRT, continuous kidney replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; PIKRT, prolonged intermittent kidney replacement therapy.

volumetric technology to precisely measure fluid flow rates, resulting in substantially more precision in volume control than achieved by standard pumps used for intravenous fluid administration. Although fluid removal with CKRT is often reported as the net ultrafiltration rate, net ultrafiltration can be described with respect to the CKRT machine or to the patient, and accurately differentiating between these two is vital. Machine net ultrafiltration is the difference between total ultrafiltration rate and the rates of pre- and/or postfilter replacement fluid, but it does not account for other patient fluid inputs or outputs and therefore does not represent the patient fluid balance. Patient fluid balance incorporates all input and output including the CKRT machine fluid balance.

Different approaches to the prescription of net ultrafiltration exist, with the most common approach being hourly adjustments by nursing in the machine net ultrafiltration rate to achieve prescribed hourly or daily goals in patient net fluid balance. Though multiple trials are ongoing, rigorous data validating the optimal approach to volume management with CKRT are lacking. For any critically ill patient requiring CKRT, nephrology and critical care providers should utilize all available data regarding hemodynamic and fluid status, ideally including dynamic measures of volume status, to guide the prescription of net ultrafiltration. In addition, the dynamic nature of critical illness requires frequent serial reassessment of ultrafiltration goals and tolerance.

### *Additional Readings*


- Friedrich JO, Wald R, Bagshaw SM, Burns KE, Adhikari NK. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. *Crit Care*. 2012;16(4):R146. doi:10.1186/cc11458
- Macedo E, Cerdá J. Choosing a CRRT machine and modality. *Semin Dial*. 2021;34(6):423-431. doi:10.1111/sdi.13029
- Murugan R, Bellomo R, Palevsky PM, Kellum JA. Ultrafiltration in critically ill patients treated with kidney replacement therapy. *Nat Rev Nephrol*. 2021;17(4):262-276. doi:10.1038/s41581-020-00358-3
- Yessayan LT, Szamosfalvi B, Rosner MH. Management of dysnatremias with continuous renal replacement therapy. *Semin Dial*. 2021;34(6):472-479. doi:10.1111/sdi.12983 ★ESSENTIAL READING


## Prescribing CKRT

### Timing of CKRT Initiation and Discontinuation

Starting CKRT too late may result in complications from AKI and volume overload. However, starting CKRT too early may expose patients who may not have truly needed KRT to its potential harms. Indeed, with the notable exception of a single-center trial that included 231 participants who were mostly postoperative ICU admissions (ELAIN study), multiple larger, multicenter RCTs assessing the timing of KRT initiation in AKI (AKIKI, IDEAL-ICU, and STARRT-AKI trials) failed to demonstrate any benefit to "accelerated" (earlier) versus "standard" (delayed) initiation. Beyond that, some signals of harm with accelerated initiation were observed, including impaired kidney recovery, more catheter-related bloodstream infections (CRBSIs), and higher rates of hypotension and hypophosphatemia. The more recent AKIKI-2 trial randomized patients to standard initiation versus "more delayed" initiation. The "more delayed" strategy resulted in a trend toward increased mortality (11% higher 60-day mortality, $P = 0.07$). Thus, no clear benefit to accelerated KRT initiation exists, yet, conversely, the results of AKIKI-2 suggest patients may be harmed by excessive delay beyond standard initiation strategies.

Consequently, the decision to initiate CKRT should take into account a variety of factors (Box 1). For most patients, CKRT should be initiated in response to concrete clinical indications: most commonly volume overload, hyperkalemia, or metabolic acidemia unresponsive to medical therapy. In patients who are appropriate candidates for escalation of care, CKRT initiation is also likely reasonable

**Box 1.** Factors to Consider When Deliberating Timing of CKRT Initiation for Patients With AKI in the ICU

Illness Severity and Trajectory and Patient Characteristics
- AKI severity and trend
- Fluid balance and symptoms of fluid overload
- Presence of oliguria, considering the response to diuretics
- Severity of electrolyte and acid-base disorders, considering the response to medical management
- Presence and severity of cardiopulmonary failure, other relevant nonrenal organ dysfunction, or underlying comorbidities impacted by AKI and/or fluid overload
- Likelihood of recovery of kidney function without KRT, considering the reversibility of the specific etiology of AKI, trends in kidney function and urine output, and baseline kidney function
- Specific scenarios frequently requiring metabolic support from high-dose CKRT (eg, rhabdomyolysis or tumor lysis syndrome)

Risks of CKRT
- Hemodynamic instability from CKRT
- Infection, including catheter-related bloodstream infection
- Other risks associated with vascular access (pneumothorax, procedural bleeding, catheter-associated deep venous thrombosis, etc)
- Clearance of trace elements, water-soluble vitamins, phosphate, amino acids/small peptides, and drugs (especially antibiotics)
- Delayed renal recovery
- Increased risk of immobilization and interference with physical rehabilitation

Patient-centered Factors
- Patient and family wishes and overall goals of care, including willingness to accept risk of long-term dialysis dependence
- Overall prognosis, including likelihood of patient survival

Health Care System Factors
- Availability of machines, disposable supplies, and nursing staff, especially during periods of strain on the health care system (eg, pandemics)
- Health care costs

Adapted from: Macedo E, Mehta RL. Continuous Dialysis Therapies: Core Curriculum 2016. *Am J Kidney Dis*. 2016;68(4):645-657. doi:10.1053/j.ajkd.2016.03.427.
Abbreviations: AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ICU, intensive care unit.

for oliguria persisting ≥48-72 hours. Notably, the overall mortality in these RCTs and many other studies of critically ill patients with AKI requiring KRT is approximately 50%. Barring an imminently life-threatening indication for KRT, consideration of CKRT initiation should usually serve as a prompt for both intensivists and nephrologists to reconsider the patient's overall prognosis. For many patients, a discussion with them or their surrogates regarding their goals of care may be carried out before obtaining consent to initiate CKRT.

Though RCTs are ongoing, no trial data currently exist to guide de-escalation of CKRT. Observational studies suggest that spontaneous urine output of >500 mL/day or diuretic-augmented urine output of >2 L/day are reasonable criteria for consideration of KRT discontinuation in patients with AKI. Ongoing need for vasopressors and higher cumulative fluid balance are associated with intradialytic hypotension in patients who transition to IHD after CKRT. In general, hemodynamic stability without vasopressor support is a commonly used trigger for consideration of transition to IHD. Experts suggest that volume overload be corrected before discontinuation or transition.

## Dose of Solute Clearance With CKRT

In contrast to IHD where pre- and posttreatment measurement of urea is used for calculations of clearance and adequacy of dose, in CKRT the total effluent flow rate ($Q_{ef}$) is used as a surrogate for clearance. $Q_{ef}$ represents the clearance by diffusion, convection, and net ultrafiltration combined (Table 5). Despite some early trials suggesting benefit with higher doses, 2 subsequent large RCTs, the VA/NIH ATN trial and the RENAL trial, found that higher doses of CKRT (35-40 mL/kg/h) had no benefit over lower doses (20-25 mL/kg/h) but were associated with somewhat higher rates of complications including hypophosphatemia and hypotension. Based on these 2 trials, the standard of care is to target a delivered CKRT dose of 20-25 mL/kg/h (Table 2). As outlined in Table 4, this standard CKRT dose provides substantially slower instantaneous clearance than IHD but a higher total daily or weekly dose of solute clearance than thrice weekly or even daily IHD.

In practice, loss of effective surface area from filter clotting/clogging, time required for filter changes, need for imaging studies and procedures outside the ICU, and other factors usually cause the achieved or delivered dose of CKRT to be lower than the prescribed dose. Observational studies suggest that delivered CKRT dose rather than prescribed dose is associated with outcomes, though this may be confounded.

To overcome the typical discrepancy between delivered dose and prescribed dose, empirically increasing the prescribed dose by 20%-25% has been recommended by some experts. However, delivered dose was somewhat lower than prescribed dose in all arms of ATN and RENAL

**Table 5.** Calculations of Total Effluent Rate, Filtration Fraction, and Dilution Factor

| Parameter | Equation |
|---|---|
| Total effluent dose ($Q_{ef}$, mL/kg/h) | CVVH: ($Q_{r,pre}$ + $Q_{r,post}$ + $UF_{net}$ [mL/h]) / weight (kg) |
| | CVVHD: ($Q_d$ + $UF_{net}$ [mL/h]) / weight (kg) |
| | CVVHDF: ($Q_{r,pre}$ + $Q_{r,post}$ + $Q_d$ + $UF_{net}$ [mL/h]) / weight (kg) |
| Plasma water flow rate ($Q_p$) | $Q_b$ (mL/min) * (1 − Hematocrit) |
| Total ultrafiltration rate ($UF_{total}$) | $Q_{r,pre}$ (mL/min) + $Q_{r,post}$ (mL/min) + $UF_{net}$ (mL/min) |
| Filtration fraction | $UF_{total}$ (mL/min) / [$Q_p$ + $Q_{r,pre}$ (mL/min)] |
| Dilution factor | $Q_p$ (mL/min) / ($Q_p$ + $Q_{r,pre}$ [mL/min]) |

$Q_{r,pre}$, $Q_{r,post}$, and $UF_{net}$ are part of total ultrafiltration ($UF_{total}$), collectively representing convective (advective) clearance, whereas $Q_d$ constitutes diffusive clearance. $UF_{net}$ refers to *machine* $UF_{net}$ and is distinct from patient fluid balance. Though $Q_b$ is traditionally prescribed in mL/min and $Q_{r,pre}$ and $Q_{r,post}$ are usually prescribed in mL/h or L/h, all flow rates must be converted to the same units to calculate filtration fraction or dilution factor. Adapted with permission of the copyright holder (John Wiley & Sons, Inc) from Neyra JA, Tolwani A. CRRT prescription and delivery of dose. *Semin Dial.* 2021;34(6):432-439. doi:10.1111/sdi.12974. Abbreviations: CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; $Q_d$, dialysate rate; $Q_{r,post}$, postfilter replacement fluid rate; $Q_{r,pre}$, prefilter replacement fluid rate; $UF_{net}$, net ultrafiltration.

trials (eg, 17.5 vs 20 mL/kg/h and 22 vs 25 mL/kg/h in the lower-dose arms, respectively). Given outcomes were equivalent with the delivery of 17.5-22 mL/kg/h in these trials, increasing prescribed dose beyond 25 mL/kg/h may be unnecessary.

Although it is controversial, it is also plausible that even lower prescribed doses of CKRT (ie, ≤20 mL/kg/h) may be noninferior. Trials are ongoing, but no RCT data currently exist to support such a strategy. Other more holistic measures of adequacy of solute clearance, such as electrolyte and acid-base homeostasis (eg, potassium concentration or pH), are likely as important as the prescribed $Q_{ef}$. The potential harms from higher delivered doses include the risk of excess or undesired removal of electrolytes (especially phosphate), micronutrients, and drugs.

The location in the circuit where replacement fluid is infused for CVVH or CVVHDF also impacts dose. With postfilter (ie, "postdilution") replacement, solute removal is maximally efficient because the solute concentration in the ultrafiltrate will be equal to the concentration in plasma water. The trade-off is that the ultrafiltration of undiluted plasma water produces significantly increased red cell and protein concentration over the filter length, increasing the risk of filter clotting. The risk of clotting related to hemoconcentration within the CKRT hemofilter is traditionally estimated by calculating the filtration fraction (FF), which is the ratio of total ultrafiltration rate over plasma water flow rate (Table 5). To lower the risk of clotting, FF should be kept at ≤20%-25% either by maintaining adequate $Q_b$ or by preferential use of prefilter replacement fluid (with the potential exception of RCA, which anecdotally permits higher FF).

With prefilter (ie, "predilution") replacement fluid, filter life is longer because the plasma water is diluted before ultrafiltration, minimizing FF. However, solute concentration is diluted before entering the filter, thereby reducing clearance somewhat. The magnitude of this effect can be estimated via calculation of a dilution factor (Table 5). Notably, FF is least when CVVHD is used, and observational and quasi-randomized data suggest CVVHD may produce a longer filter life than prefilter CVVH. Though FF is the classic parameter used to describe the effect of hemoconcentration on the risk of hemofilter clotting, recently postfilter hematocrit has been proposed as an alternative metric to predict clotting risk, though data to support the superiority of either metric are limited.

Although delivering 20-25 mL/kg/h is appropriate for most patients treated with CKRT in most circumstances, the dose should be serially reevaluated because critical illness dynamically evolves and doses of >25 mL/kg/h may occasionally be necessary. For example, in cases of rhabdomyolysis or tumor lysis syndrome, in which lack of clearance of potassium resulting from AKI is aggravated by extreme amounts of potassium being released into the circulation, CKRT doses of ≥40 mL/kg/h may be necessary to maintain metabolic control. In such cases, the high instantaneous clearance of IHD may need to be employed to initially correct life-threatening hyperkalemia, followed immediately by CKRT to provide a higher ongoing total daily dose of clearance to maintain metabolic control. In circumstances in which high-dose CKRT is used, once metabolic control is achieved and the underlying process has improved, doses should be incrementally decreased back toward the standard range to avoid excessive removal of phosphate, micronutrients, and drugs.

Though controversial, one instance in which high-dose CKRT likely should not be routinely used is for the treatment of lactic acidosis, particularly type A lactic acidosis (ie, from shock or organ-specific hypoperfusion). Although lactate, as a small water-soluble molecule, is readily dialyzed (ie, $S \approx 1$), KRT generally has minimal impact on serum lactate levels. The clearance provided, even with very high-dose CKRT (eg, 50 mL/min), is very low compared to endogenous clearance, which has been estimated in critically ill patient to be ~750-2,000 mL/min. Thus, CKRT tends to have minimal impact on serum lactate levels, and changes in levels in patients on CKRT can generally be interpreted similarly to non-CKRT patients. Though less common, KRT plays an important role in the treatment of type B lactic acidosis from drug toxicity (eg, metformin poisoning), although in that circumstance IHD is often preferred over CKRT due to higher clearance.

## Blood Flow

Compared with IHD, the typical range of $Q_b$ utilized in CKRT is significantly lower. As previously outlined, $Q_b$ typically has minimal impact on CKRT dose within the usual dose range (Table 2). However, $Q_b$ may begin to impact clearance when utilizing high-dose CKRT; in those settings, sufficient $Q_b$ relative to $Q_d$ or $Q_{r,pre}$ is necessary to maintain highly efficient solute clearance (Fig 1). Otherwise, adequate $Q_b$ is necessary to prevent hemofilter clotting.

However, although increasing $Q_b$ will always mathematically lower FF, the potential benefit for increased filter life eventually diminishes with further increases in $Q_b$ (likely beyond ~250 mL/min). For example, 1 trial randomized 100 patients receiving CKRT without anticoagulation or with heparin to $Q_b$ of 150 or 250 mL/min and found no difference in filter life. This likely results from the fact that, for a given circuit resistance, higher $Q_b$ also increases the risk of pressure alarms. Such pressure alarms trigger blood pump stoppages or reductions which may, when recurrent, promote filter clotting.

Finally, when utilizing RCA, lower $Q_b$ (eg, 120-150 mL/min) is generally recommended. This is both because a lower citrate dose will be required to maintain adequate anticoagulation, in turn minimizing risk of metabolic complications of RCA, and because RCA is effective enough to maintain filter patency despite lower $Q_b$.

## Additional Readings


- Baldwin I, Bellomo R, Koch B. Blood flow reductions during continuous renal replacement therapy and circuit life. *Intensive Care Med*. 2004;30(11):2074-2079. doi:10.1007/s00134-004-2440-0
- Beaubien-Souligny W, Yang Y, Burns KEA, et al. Intradialytic hypotension following the transition from continuous to intermittent renal replacement therapy. *Ann Intensive Care*. 2021;11:96. doi:10.1186/s13613-021-00885-7
- Clark EG, Vijayan A. Intensive RRT for AKI: dial down your enthusiasm! *Kidney360*. 2022;3(8):1439-1441. doi:10.34067/KID.0000972022
- Gaudry S, Hajage D, Martin-Lefevre L, et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. *Lancet*. 2021;397(10281):1293-1300. doi:10.1016/S0140-6736(2100350-0)
- Hatamizadeh P, Tolwani A, Palevsky P. Revisiting filtration fraction as an index of the risk of hemofilter clotting in continuous venovenous hemofiltration. *Clin J Am Soc Nephrol*. 2020;15(11):1660-1662. doi:10.2215/CJN.02410220
- Levraut J, Ciebiera JP, Jambou P, Ichai C, Labib Y, Grimaud D. Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. *Crit Care Med*. 1997;25(1):58-62. doi:10.1097/00003246-199701000-00013
- Mann L, Ten Eyck P, Wu C, et al. CVVHD results in longer filter life than pre-filter CVVH: results of a quasi-randomized clinical trial. *PLoS One*. 2023;18(1):e0278550. doi:10.1371/journal.pone.0278550
- Ostermann M, Bagshaw SM, Lumlertgul N, Wald R. Indications for and timing of initiation of KRT. *Clin J Am Soc Nephrol*. 2023;18(1):113-120. doi:10.2215/CJN.05450522
- RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361(17):1627-1638. https://doi.org/10.1056/NEJMoa0902413 ★ESSENTIAL READING
- STARRT-AKI Investigators, Canadian Critical Care Trials Group, Australian New Zealand Intensive Care Society Clinical Trials Group, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med*. 2020;383(3):240-251. https://doi.org/10.1056/NEJMoa1803213 ★ESSENTIAL READING
- VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):7-20. https://doi.org/10.1056/NEJMoa0802639 ★ESSENTIAL READING


## Maintaining the CKRT Circuit

### Vascular Access

***Case 2:*** *A 56-year-old man with end-stage kidney disease (ESKD) on maintenance IHD via a left arm arteriovenous fistula (AVF), diabetes, obesity with body mass index (BMI) 42 kg/m², and congestive heart failure presents to the emergency department with dyspnea after missing several dialysis treatments due to malaise. He is diagnosed with an ST elevation myocardial infarction and cardiogenic shock and undergoes endotracheal intubation. Coronary angiography reveals multivessel disease, and he undergoes stenting of his left anterior descending coronary artery with plans for eventual coronary artery bypass surgery after stabilization. After his procedure, he arrives to the ICU with ongoing refractory shock requiring mechanical cardiac support with a percutaneous left ventricular assist device and infusions of epinephrine, norepinephrine, vasopressin, and cangrelor. On examination, he weighs 165 kg and is 198-cm tall; he has a large abdominal pannus, 3-4+ pitting edema extending to the thighs, and a loud bruit and a strong thrill at his AVF. His laboratory results include potassium, 6.2 mEq/L; serum urea nitrogen (SUN), 98 mg/dL; lactate, 7.2 mmol/L; and arterial blood gas (ABG) with pH 7.12, $P_{CO_2}$, 48 mm Hg; and $Pa_{O_2}$, 71 mmHg on 90% oxygen. The chest X-ray shows severe pulmonary edema. The ICU resident begins to place a right internal jugular (IJ) temporary dialysis catheter but finds the vein to be occluded with thrombus.*

**Question 2: Which of the following is the most appropriate next step?**

(a) Perform a 4-hour session of IHD through the AVF.
(b) Initiate CKRT using needle cannulation of the AVF.
(c) Initiate CKRT using a dialysis catheter placed in his left IJ to a depth of 16 cm.
(d) Initiate CKRT using a dialysis catheter placed in his left IJ to a depth of 24 cm.
(e) Initiate CKRT using dialysis catheter placed in his right femoral vein.

*For the answer to this question, see the following text.*

A well-functioning vascular access, in the form of either a temporary or tunneled cuffed dual-lumen hemodialysis catheter, is required for effective CKRT. The catheter needs to be capable of achieving a $Q_b$ of at least 200 mL/min.

In ESKD patients with a pre-existing AVF or arteriovenous graft (AVG), use of the AVF or AVG for CKRT should generally be avoided unless catheter placement proves impossible. Due to lower $Q_b$ and the continuous nature of CKRT, increased risks exist for needle dislodgment with possible exsanguination, access thrombosis, or permanent damage to the vascular access.

Bedside placement of temporary hemodialysis catheters should be performed using real-time ultrasound guidance for both IJ and femoral sites. Regarding site selection for catheter insertion, Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines suggest the following order of preference: (1) right IJ, (2) femoral, and (3) left IJ. However, as will be outlined further, some experts recommend preferential use of left IJ over femoral sites in obese patients. Subclavian sites should be reserved as the last option because observational studies in ESKD patients suggest an increased risk of central venous stenosis.

Heparin or trisodium citrate can be used as catheter-locking solutions after catheter insertion and before CKRT initiation or during interruptions in therapy. Studies suggest that trisodium citrate is superior to heparin because it is associated with lower bleeding, thrombosis, and infection rates. The routine use of antibiotic-impregnated catheters, topical antibiotics, or antibiotic locks are not recommended because they may promote fungal infections and antimicrobial resistance.

Contrary to historical opinion, more recent data suggest that the risk of infection with temporary femoral catheters is not significantly higher than with temporary IJ catheters, but this equivalence appears to be restricted to nonobese patients. Specifically, in the CATHEDIA trial—which randomized 750 patients requiring acute KRT to femoral or IJ catheter placement—the overall rates of catheter colonization or CRBSI were similar in both groups, but the rate of catheter colonization was lower with temporary femoral catheters in patients in the lowest BMI tercile ($<24.2$ kg/m$^2$) compared with the highest tercile ($>28.4$ kg/m$^2$). Conversely, those in the highest BMI tercile were found to have more catheter colonization with femoral catheters than with IJ catheters.

Routine catheter exchanges are not effective at reducing the CRBSI risk and are not recommended. Once it becomes clear that recovery of kidney function to KRT independence is not imminent, fluoroscopy-guided insertion of a tunneled, cuffed hemodialysis catheter should be considered.

Rewiring of temporary hemodialysis catheters for catheter dysfunction is often ineffective and, in many cases, placement at a new site may save time and result in improved catheter function.

Regarding Case 2, IHD using vasopressor support is reasonable in ESKD patients with a functioning AVF to avoid placement of a catheter, especially if the degree of vasopressor support is relatively low (eg, 1-2 pressors at low-to-moderate dose), the shock is anticipated to be of relatively short duration (eg, few days or less), and the need for volume removal is modest. However, the severity of shock in this case would preclude using IHD at most institutions. Furthermore, with severe hypoxemia and anasarca, 4 hours of IHD is unlikely to prove adequate to improve his volume status, which makes (a) incorrect. Although PIKRT via his AVF might be reasonable if CKRT is unavailable, CKRT would be the most effective modality to address his severe volume overload in the setting of shock. Furthermore, as previously outlined, most centers do not use AVFs/AVGs for CKRT, so (b) is incorrect.

Although the right IJ vein is always preferred when available, the choice between femoral and left IJ placement is less straightforward. Trial data suggest that the overall rate of infection with femoral placement of temporary dialysis catheters is similar to jugular placement with modern infection-prevention practices; however, this equivalence has not been observed in obese patients, in whom the femoral site had higher rates of bacteremia or catheter colonization. Moreover, femoral catheters are more likely to malfunction in obese patients, and thus (e) is incorrect. Instead, some experts consider left IJ preferable to femoral placement in obese patients so long as care is taken to ensure the tip of the catheter reaches the cavoatrial junction.

A 16-cm left IJ catheter is unlikely to be adequate, especially in a 198-cm tall patient, so (c) is incorrect. Though not extensively validated, a reasonable method to estimate adequate depth of IJ placement is Height (cm) / 10 for right IJ and (Height [cm] / 10) + 4 cm for left IJ placement. In this case, with a nearly 200-cm-tall patient, targeting 24 cm of depth for a left IJ is reasonable, so (d) is correct.

### Anticoagulation

***Case 3:*** *A 42-year-old man with cirrhosis is initiated on CKRT for oliguric AKI with hyperkalemia and metabolic acidosis in the setting of hemorrhagic shock from variceal hemorrhage. He weighs 80 kg and is prescribed CVVHD with $Q_d$ 2,000 mL/min. After 48 hours, the metabolic abnormalities are improved, and his bleeding has stopped with endoscopic banding of his esophageal varices, but he remains oliguric, on mechanical ventilation, and on infusions of octreotide, norepinephrine (0.12 μg/kg/min), and vasopressin (0.03 units/min). His laboratory results now include potassium, 4.2 mEq/L; SUN, 68 mg/dL; lactate, 2.8 mmol/L; and ABG with pH 7.38; $P_{CO_2}$, 35 mm Hg; and $P_{aO_2}$, 72 mm Hg on 80% oxygen. However, since starting CKRT he has required 4 circuit changes due to hemofilter clotting. Per his nurse, the hemodialysis catheter has been functioning well without any access pressure or return pressure alarms. The examination is notable for 2-3+ generalized edema and obvious ascites. In the last 24 hours, his urine output has been 145 mL with net positive fluid balance of 630 mL due*

*in part to the interruptions in CKRT treatment caused by hemofilter clotting. The chest X-ray shows moderately severe pulmonary edema and appropriate positioning of the catheter tip at the cavoatrial junction. The ICU team is continuing to hold pharmacologic venous thromboembolism prophylaxis because gastroenterology is concerned that his rebleeding risk remains high.*

**Question 3: Which of the following is the next best step?**

(a) Stop CKRT and manage any further metabolic abnormalities with medical therapy.
(b) Transition to IHD without anticoagulation.
(c) Restart CKRT with regional citrate anticoagulation (RCA) and close lab monitoring.
(d) Restart CKRT without anticoagulation.

*For the answer to this question, see the following text.*

Though the 2012 KDIGO guidelines for AKI recommend use of anticoagulation to prolonger filter life, a substantial proportion of centers (approximately 33%-50%) start CKRT without anticoagulation, with the addition of anticoagulation if premature hemofilter clotting develops. The two most commonly used anticoagulants for CKRT are heparin and citrate.

Heparin has the advantages of being inexpensive and familiar. Heparin can be provided via a separate infusion or within the CKRT circuit in the prefilter segment, with the latter being preferable as it increases intrafilter heparin concentration. However, heparin is not dialyzable and even prefilter heparin results in systemic anticoagulation (unless coupled with a reversal agent). Less commonly, heparin is used with the reversal agent protamine to produce regional anticoagulation. Not surprisingly, use of heparin anticoagulation without reversal is associated with increased bleeding risk.

In contrast, RCA produces no systemic anticoagulant effect. In RCA, citrate is delivered in the pre-filter segment of the circuit, typically targeting a goal blood citrate concentration of 3-6 mmol/L, and chelates calcium to generate a low intra-filter ionized calcium concentration (typically <0.4 mmol/L) to inhibit the clotting cascade. Usually most of the citrate is removed in the CKRT effluent, though a variable but substantial proportion is delivered to the patient where it is metabolized primarily by the liver. To reverse the effect of citrate, to replace the calcium lost as citrate-calcium complexes, and to prevent life-threatening hypocalcemia in the patient, intravenous calcium is continuously infused into the return limb of the CKRT circuit or via a separate systemic infusion. Typical RCA protocols involve serial monitoring of both filter and systemic ionized calcium to allow for titration of the citrate and calcium infusions. If the filter ionized calcium is above goal the citrate infusion rate is increased, and vice versa. Likewise, if the systemic ionized calcium concentration is low the calcium infusion rate is increased, and vice versa. Finally, as described further below, total calcium should be monitored at least daily to monitor for citrate accumulation. Various formulations of citrate anticoagulation are available (Table 3), each requiring specific protocols for use.

Though historically considered a contraindication to RCA, emerging data suggest that RCA can be used in the setting of liver disease with careful monitoring. Notably, the disordered coagulation of liver disease is associated with an increased risk of bleeding and clotting such that liver disease is associated with reduced CKRT filter life. Protocols have been developed specifically to minimize the risk of citrate accumulation when used in the setting of absent citrate metabolism. A more useful metric than measures of hepatic function to determine the risk of citrate accumulation is lactate level. Like citrate, lactate is an organic anion normally metabolized primarily by the liver, and lactate elevations, regardless of cause (eg, shock or liver disease), imply impaired lactate metabolism and risk of impaired citrate metabolism. As a rough guide, serum lactate <4 mmol/L, 4-8 mmol/L, and >8 mmol/L suggest low, intermediate, and high risk, respectively, of citrate accumulation.

While RCA comes at the expense of increased complexity and need for more frequent laboratory monitoring, the superiority of RCA over systemic heparin in prolonging hemofilter life and preventing bleeding complications has been repeatedly demonstrated in trials. The most recent and largest of these was the multicenter RICH trial, which randomized nearly 600 patients to systemic heparin or RCA and found that RCA produced significantly longer filter life by 15 hours, fewer bleeding events, and no significant difference in mortality.

Less common options for CKRT circuit anticoagulation include direct thrombin inhibitors and nafamostat mesylate (a serine protease inhibitor used for decades in East Asia), but large RCTs evaluating their use are currently lacking.

Returning to Case 3, liver disease alone is not a contraindication to RCA, especially now that his serum lactate is minimally elevated, and restarting CKRT without anticoagulation is likely to lead to ongoing premature filter loss, and thus (d) is incorrect. Given that he remains oliguric, volume overloaded, severely hypoxemic, and in shock, continuing CKRT with the addition of RCA with careful laboratory monitoring, answer (c), is the most appropriate. Stopping KRT altogether is unlikely to be well tolerated, and IHD is unlikely to be effective in treating his volume overload, especially in the setting ongoing oliguria and requirement for 2 vasopressors, which makes (a) and (b) incorrect. Finally, as implied in Case 3, because catheter dysfunction is a common cause of circuit clotting, the first step in the evaluation of recurrent clotting—before considering anticoagulation—is evaluation of the vascular access.

### Additional Readings

➢ Clark EG, Barsuk JH. Temporary hemodialysis catheters: recent advances. *Kidney Int.* 2014;86(5):888-895. doi:10.1038/ki.2014.162

- Coupez E, Timsit JF, Ruckly S, et al. Guidewire exchange vs new site placement for temporary dialysis catheter insertion in ICU patients: is there a greater risk of colonization or dysfunction? *Crit Care*. 2016;20(1):230. doi:10.1186/s13054-016-1402-6
- Davenport A, Tolwani A. Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. *NDT Plus*. 2009;2(6):439-447. doi:10.1093/ndtplus/sfp136 ★ESSENTIAL READING
- Parienti JJ, Megarbane B, Fischer MO, et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled study. *Crit Care Med*. 2010;38(4):1118-1125. doi:10.1097/CCM.0b013e3181d454b3
- Parienti JJ, Thirion M, Megarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA*. 2008;299(20):2413-2422. doi:10.1001/jama.299.20.2413 ★ESSENTIAL READING
- Szamosfalvi B, Puri V, Sohaney R, et al. Regional citrate anticoagulation protocol for patients with presumed absent citrate metabolism. *Kidney360*. 2021;2(2):192-204. doi:10.34067/KID.0005342020
- Zarbock A, Kullmar M, Kindgen-Milles D, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury: a randomized clinical trial. *JAMA*. 2020;324(16):1629-1639. doi:10.1001/jama.2020.18618 ★ESSENTIAL READING
- Zhang W, Bai M, Yu Y, et al. Safety and efficacy of regional citrate anticoagulation for continuous renal replacement therapy in liver failure patients: a systematic review and meta-analysis. *Crit Care*. 2019;23(1):22. doi:10.1186/s13054-019-2317-9


## Complications of CKRT

***Case 3, continued:*** *Over the next 48 hours, the patient has no additional episodes of hemofilter loss. He is receiving anticoagulant citrate dextrose solution-A (ACD-A) at 230 mL/h with 0.8% calcium chloride at 90 mL/h. He remains on CVVHD with $Q_b$ 150 mL/min with calcium-free dialysate running at 2,000 mL/h. Otherwise, he remains oliguric, on vasopressor support, and on mechanical ventilation without recurrent bleeding. However, he has developed hypercalcemia and his nurse is concerned about citrate toxicity. His laboratory results include potassium, 3.8 mEq/L; bicarbonate, 29 mEq/L; SUN, 42 mg/dL; phosphate, 1.8 mg/dL; albumin, 3.0 g/dL; total calcium, 11.1 mg/dL; systemic ionized calcium, 1.48 mmol/L; postfilter ionized calcium, 0.42 mmol/L; lactate, 1.6 mmol/L; and ABG with pH, 7.46; $P_{CO_2}$, 43 mm Hg; and $Pa_{O_2}$, 68 mm Hg on 60% oxygen.*

**Question 4: Which of the following is the most appropriate step to correct his hypercalcemia?**

(a) Stop CKRT.
(b) Continue CKRT but change anticoagulation to pre-filter heparin.
(c) Continue CKRT but increase the dialysate rate to 3,000 mL/h.
(d) Continue CKRT with RCA, but decrease the rate of ACD-A to 210 mL/h.
(e) Continue CKRT with RCA, but decrease the rate of calcium chloride to 80 mL/h.

*For the answer to this question, see the following text.*

Most complications of CKRT can be categorized into metabolic disturbances, access-related complications, and those related to the extracorporeal circuit (Box 2). Severe allergic reactions to the hemofilter or circuit tubing and circuit-related hemolysis have been described but are rare. Though anecdotally appreciated for years, recent observational data confirm an association between CKRT and thrombocytopenia in patients treated with CKRT. However, the degree of decline is usually relatively modest (ie, 33%-50% from baseline), and CKRT as the cause of thrombocytopenia should be considered a diagnosis of exclusion given the many other potential causes of thrombocytopenia in critically ill patients.

Though highly effective, RCA can induce a variety of metabolic complications. Given that each citrate molecule is metabolized into 3 bicarbonate molecules, the most common is metabolic alkalosis, which may be referred to as citrate excess or buffer excess but is distinct from citrate accumulation. Alkalosis related to RCA can be treated by decreasing $Q_b$ and citrate rate in parallel (which will maintain an adequate blood citrate concentration but decrease the total citrate load delivered to the patient); by increasing the CKRT dose by increasing the rate of citrate-free dialysate and/or replacement fluid (to enhance citrate extraction by the hemofilter); and/or by decreasing the bicarbonate concentration of the other CKRT solutions. Otherwise, isolated ionized hypocalcemia or hypercalcemia is relatively common and usually is corrected by adjustment in the rate of the postfilter or systemic calcium replacement infusion. Though variable, some commonly used formulations of citrate (eg, trisodium citrate and ACD-A) are hypertonic and can cause mild hypernatremia (Table 3). Finally, RCA can cause hypomagnesemia as citrate weakly chelates magnesium.

The most feared complication of RCA is citrate accumulation, which is also referred to as citrate toxicity or citrate lock. As most clinical laboratories do not measure plasma citrate levels, the ratio of total calcium (tCa) to ionized calcium (iCa) is used as a surrogate measure of citrate levels. Because normally approximately 50% of total calcium is ionized, this ratio is usually 2-1, though

**Box 2.** Overview of CKRT Complications

Complications Related to Catheter Placement
- Hematoma, hemorrhage, or traumatic arteriovenous fistula
- Infection (CRBSI or local soft tissue infection)
- Vein thrombosis or stenosis
- Pneumothorax or hemothorax
- Air embolism
- Visceral injury

Complications Related to Extracorporeal Circuit
- Allergic reaction to dialyzer/hemofilter or circuit tubing (rare)
- Circuit thrombosis
- Hemolysis
- Air embolism
- Hypothermia
- Thrombocytopenia

Metabolic Disturbances
- Complications of regional citrate anticoagulation:
  - ◇ Citrate accumulation, ie, citrate toxicity or citrate lock (see text)
  - ◇ Citrate/buffer excess or citrate/buffer deficit (see text)
  - ◇ Isolated hypo- or hypercalcemia
  - ◇ Hypernatremia (if using formulation containing trisodium citrate)
  - ◇ Hypomagnesemia
- Hypophosphatemia, possibly aggravating respiratory muscle weakness
- Others: hypokalemia, hypocalcemia, hypomagnesemia
- Hypoglycemia (when using dextrose-free CKRT solutions)
- Euglycemic ketoacidosis (when using dextrose-free CKRT solutions)

Others
- Hypotension, especially with initiation or net ultrafiltration
- Inappropriate (excess or inadequate) medication dosing
- Inadequate nutrition due to nonselective clearance of amino acids and other micronutrients

Adapted with permission of the copyright holder (Wolters Kluwer Health) from Teixeira JP, Neyra JA, Tolwani A. Continuous KRT: a contemporary review. *Clin J Am Soc Nephrol*. 2023;18(2):256-269. doi:10.2215/CJN.04350422. Abbreviations: CRBSI, catheter-related bloodstream infection; CKRT, continuous kidney replacement therapy.

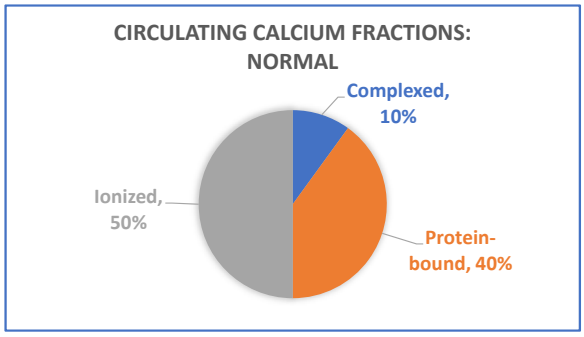
notably in US hospitals total and ionized calcium are often (but not always) measured in different units (Fig 2). Significant citrate accumulation will cause citrate-calcium complexes to accumulate, resulting in an increase in tCa and/or a decrease in iCa, with a tCa/iCa ratio of ≥2.5. Notably, correction of the total calcium for hypoalbuminemia is not generally recommended and, based on at least 1 study, likely unnecessary. Though a somewhat later finding than the increase in tCa/iCa ratio, eventually citrate accumulation will also produce a clinically appreciable increase in anion gap. Such an increase in anion gap is by definition an acidosis, but typically enough accumulated citrate is metabolized to bicarbonate that frank acidemia (though possible) is uncommon if citrate accumulation is diagnosed early (ie, typically a complex acid-base disorder develops with anion gap metabolic acidosis, counterbalancing metabolic alkalosis, and roughly normal pH).

When not using RCA, other metabolic disturbances from CKRT may include hypokalemia, hypomagnesemia, and hypocalcemia. However, these are mitigated by fact that most CKRT solutions contain physiologic concentrations of potassium, magnesium, and calcium. By contrast, most commercially available CKRT solutions contain no phosphate, making hypophosphatemia common with CKRT. The increased risk of hypophosphatemia with CKRT compared with IHD relates to the intercompartmental kinetics of phosphate. Similar to potassium, most phosphate is located intracellularly; but, unlike potassium which exists inside cells primarily as a free ion, most intracellular phosphate is covalently bound to proteins and other molecules such that intracellular phosphate only slowly equilibrates with the extracellular compartment. Consequently, the primary determinant of phosphate removal with KRT is duration of treatment. Though IHD effectively clears the extracellular compartment of phosphate, only a modest amount of total body phosphate is removed with a single IHD session. In contrast, the continuous nature of CKRT overcomes the slow redistribution of phosphate, usually resulting in hypophosphatemia within approximately 48 hours of CKRT initiation with phosphate-free CKRT solutions.

Severe hypophosphatemia can induce a variety of complications, including muscle weakness, rhabdomyolysis, and myocardial depression. Additionally, CKRT-induced hypophosphatemia has been associated with prolonged mechanical ventilation or an increased need for tracheostomy. Although data proving that prevention of hypophosphatemia improves outcomes are lacking, measures to mitigate CKRT-induced hypophosphatemia are nonetheless recommended. Options include use of phosphate-containing CKRT solutions or the pre-emptive initiation of scheduled phosphate replacement as soon as the initial AKI-induced hyperphosphatemia is corrected. Premanufactured phosphate-containing CKRT solutions were approved by the US Food and Drug Administration in 2015 (Table 3). Alternatively, pharmacists may compound such solutions by adding phosphate to traditional phosphate-free solutions, or, in some cases, phosphate additives can be directly added to commercially available solutions.

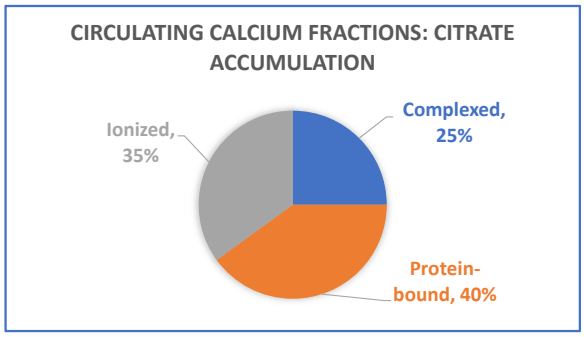
Finally, in contrast to most other CKRT solutions which contain physiologic concentrations of glucose, the commercially available CKRT solutions containing phosphate are devoid of glucose, creating the potential for additional complications in patients not receiving nutrition or another glucose source—namely, hypoglycemia or euglycemic ketoacidosis. The latter manifests with unexplained anion gap metabolic acidosis, normal serum glucose, and ketonemia and requires treatment with infusions of dextrose and insulin. Thus, in patients on CKRT who develop high anion gap acidosis without elevated lactate or citrate accumulation, euglycemic ketoacidosis must always be considered.

A




| Calcium Levels in Differing Units: Normal | | | | |
|---|---|---|---|---|
| | % | mmol/L | mEq/L | mg/dL |
| $iCa^{++}$ | 50% | 1.25 | 2.5 | 5 |
| $tCa^{++}$ | 100% | 2.5 | 5 | 10 |
| $tCa^{++}/iCa^{++}$ | 2-to-1 | | | |

B




| Calcium Levels in Differing Units: Citrate Accumulation | | | | |
|---|---|---|---|---|
| | % | mmol/L | mEq/L | mg/dL |
| $iCa^{++}$ | 35% | 0.96 | 1.92 | 3.84 |
| $tCa^{++}$ | 100% | 2.75 | 5.5 | 11 |
| $tCa^{++}/iCa^{++}$ | 2.9-to-1 | | | |

C

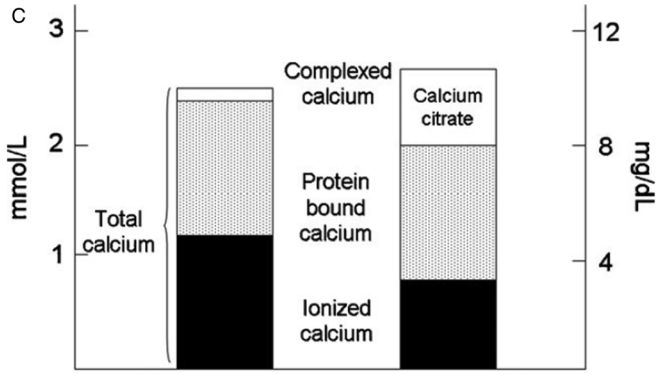



**Figure 2.** Circulating fractions of calcium under normal conditions and during citrate accumulation. (A) Normally approximately 50% of circulating plasma calcium is free; approximately 40% is bound to proteins (mostly albumin); and approximately 10% is complexed with other smaller molecules, such as phosphate, bicarbonate, and citrate, the latter of which is normally present at low physiologic levels. The ionized calcium is both biologically active and is diffusible. Therefore, ionized calcium enters equilibrium with dialysate during dialysis such that KRT prescribed with a typical calcium dialysate (or replacement fluid) concentration of 2.5 mEq/L will tend to pull serum ionized calcium toward 1.25 mmol/L. (B) In the setting of citrate accumulation (ie, citrate toxicity or citrate lock), the levels of ionized calcium drop while the fraction of complexed calcium increases significantly. Because the fraction of complexed calcium is not directly measured, citrate accumulation is detected indirectly via an increase in the ratio of total calcium to ionized calcium from a normal baseline of approximately 2 to ≥2.5. (C) The fractions of calcium under normal conditions and in the setting of citrate accumulation in bar graph form. Abbreviations: $iCA^{++}$, ionized calcium; $tCA^{++}$, total calcium. Panel C is released under a Creative Commons CC-BY-NC license from: Davenport A, Tolwani A. Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. *NDT Plus* 2009;2(6):439-447. doi: 10.1093/ndtplus/sfp136.

Regarding Question 4, both the systemic ionized calcium and total calcium are high. When converting both values to the same units, the ratio of total calcium (11.1 mg/dL = 2.78 mmol/L) to ionized calcium (1.48 mmol/L) is 1.88, which is not consistent with citrate accumulation and thus stopping CKRT or RCA is unnecessary, so (a) and (b) are incorrect. Instead, too much calcium replacement is being delivered and the rate of calcium chloride should be decreased; thus, (e) is correct. Decreasing the rate of citrate is unnecessary and not advised because the postfilter ionized calcium is slightly above goal of 0.4 mmol/L, so (d) is incorrect; in addition, the postfilter ionized calcium will tend to drop somewhat as one lowers the calcium replacement rate. Finally, increasing this patient's dialysate rate above the recommended range of 25 mL/kg/h is unnecessary without a

clear need for increased clearance and, in this case, will only aggravate his hypophosphatemia and metabolic alkalosis, which makes (c) incorrect.

### Additional Readings


- Akhoundi A, Singh B, Vela M, et al. Incidence of adverse events during continuous renal replacement therapy. *Blood Purif*. 2015;39(4):333-339. doi:10.1159/000380903
- Griffin BR, Jovanovich A, You Z, Palevsky P, Faubel S, Jalal D. Effects of baseline thrombocytopenia and platelet decrease following renal replacement therapy initiation in patients with severe acute kidney injury. *Crit Care Med*. 2019;47(4):e325-e331. doi:10.1097/CCM.0000000000003598
- Heung M, Mueller BA. Prevention of hypophosphatemia during continuous renal replacement therapy—an overlooked problem. *Semin Dial*. 2018;31:213-218. doi:10.1111/sdi.12677
- Thompson Bastin ML, Stromberg AJ, Nerusu SN, et al. Association of phosphate-containing versus phosphate-free solutions on ventilator days in patients requiring continuous kidney replacement therapy. *Clin J Am Soc Nephrol*. 2022;17(5):634-642. doi:10.2215/CJN.12410921


## Multidisciplinary Care of the Patient Requiring CKRT

### Drug Dosing

Though variable, because CKRT typically provides a total daily dose of clearance that is lower than normal kidney function but substantially higher than IHD (Table 4), the required doses of dialyzable medications provided to patients on CKRT will usually be more than the doses recommended for IHD but less than the doses recommended for normal kidney function. In any given patient, the achieved drug levels will depend on multiple factors including CKRT dose, residual kidney function, degree of hemofilter adsorption, and changes in volume of distribution and protein binding which are common in critical illness. Predicting drug levels is therefore challenging, and patients undergoing CKRT often experience over- and underdosing of medications, which carries risk of substantial harm, especially when considering dialyzable antimicrobial agents in patients with sepsis. Coordination with critical care pharmacists knowledgeable in CKRT is essential, with therapeutic drug monitoring recommended whenever feasible.

### Nutrition and Physical Rehabilitation

CKRT may contribute significantly to the negative nitrogen balance that is typically seen with the inflammatory insults and catabolic states characteristic of critical illness. In contrast with intact kidneys, in which amino acids and small peptides are filtered at the glomerulus but fully reabsorbed by the proximal tubule, CKRT can lead to the nonselective loss of 10-20 g of amino acids daily along with other water-soluble micronutrients. Though additional data are needed, this amino acid removal by CKRT may plausibly aggravate ICU-acquired weakness. To overcome this loss, daily nutritional targets of 25-35 kcal/kg total calories and 1.5-2.5 g/kg of protein are recommended in patients receiving CKRT. Likewise, though many perceive CKRT to be a barrier to mobilization, observational studies have shown that cautious physical rehabilitation is feasible and safe in patients undergoing CKRT, and nephrologists should advocate that physical therapy is provided to CKRT patients who are otherwise appropriate candidates for early mobilization.

### Monitoring CKRT Performance

With mortality of approximately 50%, critically ill patients with AKI requiring CKRT are at high risk of adverse outcomes. Thus, to ensure patients receive the highest possible quality of care, quality assurance initiatives should be embedded into CKRT programs. Quality measures have only recently been

| Key Performance Indicator (KPIs) | Definition | Proposed Benchmark |
|---|---|---|
| CKRT Leadership | Presence of both CKRT medical and nursing leads | 100% |
| CKRT Education | Number of CKRT providers with training and certification | 100% |
| Filter Life | Number of filters lasting >60 h | >60% |
| Down-time | Percentage of time CKRT not running during prescribed time | <15% |
| Delivered Dose | (Actual delivered dose / 24 h)/(Prescribed Dose / 24 h) | >80% |
| Ultrafiltration Realized | (Net ultrafiltration achieved / 24 h) / (Net ultrafiltration prescribed / 24 h) | >80% |
| ICU Mortality | Patient survival to ICU discharge | >50% |
| Renal Recovery | Percentage of patients not requiring KRT at 90 days | >90% |

**Figure 3.** Examples of proposed KPIs for CKRT programs. CKRT KPIs are shaded from white to light to dark grey across the Donabedian model of structure, process, and outcome quality measures. Benchmarks based on previous work are proposed but need to be better validated through prospective trials and must be adapted to local logistics and program-specific historical performance. Abbreviations: CKRT, continuous kidney replacement therapy; ICU, intensive care unit; KPI, key performance indicator.

developed and implemented in CKRT care. A 2017 systematic review identified multiple possible quality measures from the literature, but significant heterogeneity existed in the reporting, evaluation, and definition of these measures. The same group further defined, ranked, and prioritized these proposed quality measures into key performance indicators (KPIs) for CKRT care and organized them into a framework of *structure*, *process*, and *outcome* measures (Fig 3).

Several examples of successful CKRT quality assurance programs have been published. Mottes et al created a CKRT dashboard to monitor process and outcome metrics—including filter life, delivered versus prescribed dose, delivered versus prescribed net ultrafiltration, and survival—in a pediatric CKRT program and showed that, by doing so, efficiencies can be created and improved performance achieved. Ruiz et al demonstrated in an adult CKRT program that, by monitoring similar KPIs and providing targeted education based on audit and feedback reports focusing on the poorest performing KPIs, improvements can be achieved in filter life, alarm frequency, and cost while maintaining similar patient outcomes.

Additional research is ongoing to determine which KPIs are most impactful on patient-centered and health care system outcomes and to validate the best approaches to CKRT quality program implementation. Meanwhile, local patient demographics and practice patterns, local information technology infrastructure and expertise, and baseline KPI data should all be considered when implementing CKRT quality programs.

## Additional Readings


- Lewis SJ, Mueller BA. Antibiotic dosing in patients with acute kidney injury: "enough but not too much." *J Intensive Care Med*. 2016;31(3):164-176. doi:10.1177/0885066614555490
- Mayer KP, Joseph-Isang E, Robinson LE, Parry SM, Morris PE, Neyra JA. Safety and feasibility of physical rehabilitation and active mobilization in patients requiring continuous renal replacement therapy: a systematic review. *Crit Care Med*. 2020;48(11):e1112-e1120. doi:10.1097/CCM.0000000000004526 ★ESSENTIAL READING
- Mottes TA, Goldstein SL, Basu RK. Process based quality improvement using a continuous renal replacement therapy dashboard. *BMC Nephrol*. 2019;20(1):17. doi:10.1186/s12882-018-1195-8
- Ostermann M, Lumlertgul N, Mehta R. Nutritional assessment and support during continuous renal replacement therapy. *Semin Dial*. 2021;34(6):449-456. doi:10.1111/sdi.12973
- Rewa OG, Eurich DT, Noel Gibney RT, Bagshaw SM. A modified Delphi process to identify, rank and prioritize quality indicators for continuous renal replacement therapy (CRRT) care in critically ill patients. *J Crit Care*. 2018;47:145-152. doi:10.1016/j.jcrc.2018.06.023 ★ESSENTIAL READING
- Rewa OG, Villeneuve PM, Lachance P, et al. Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: a systematic review. *Intensive Care Med*. 2017;43(6):750-763. doi:10.1007/s00134-016-4579-x
- Roberts DM, Roberts JA, Roberts MS, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. *Crit Care Med*. 2012;40(5):1523-1528. doi:10.1097/CCM.0b013e318241e553 ★ESSENTIAL READING
- Ruiz EF, Ortiz-Soriano VM, Talbott M, et al. Development, implementation and outcomes of a quality assurance system for the provision of continuous renal replacement therapy in the intensive care unit. *Sci Rep*. 2020;10(1):20616. doi:10.1038/s41598-020-76785-w
- Teixeira JP, Mayer KP, Griffin BR, et al. Intensive care unit-acquired weakness in patients with acute kidney injury: a contemporary review. *Am J Kidney Dis*. 2023;81(3):336-351. doi:10.1053/j.ajkd.2022.08.028


## Article Information

**Authors' Full Names and Academic Degrees:** J. Pedro Teixeira, MD, Swapnil Hiremath, MD, MSc, Abdulghani Omar Kabli, MD, Oleksa G. Rewa, MD, and Edward G. Clark, MD, MSc.

**Authors' Affiliations:** Divisions of Nephrology and Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico (JPT); Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada (SH, AOK, EGC); and Department of Critical Care Medicine, University of Alberta, Edmonton, Canada (OGR).

**Address for Correspondence:** Edward G. Clark, MD, MSc, Ottawa Hospital, Riverside Campus, 1967 Riverside Dr, Ottawa, ON, Canada K1S 0V3. Email: edclark@toh.ca

**Support:** None.

**Financial Disclosure:** Dr Teixeira has received consulting fees from Outset Medical and owns stock and/or options in Eli Lilly, Novo Nordisk A/S, and Pfizer. Dr Rewa has received consulting fees from Baxter Healthcare Inc. The other authors declare that they have no relevant financial interests.

**Acknowledgements:** The authors gratefully acknowledge that this updated Core Curriculum rests on the shoulders of giants: Dr Etienne Macedo and Dr Ravindra L. Mehta, the authors of "Continuous Dialysis Therapies: Core Curriculum 2016," provided the foundation for much of this update. For many sections, we hewed closely to their text, formatting, and tables. The authors also greatly appreciate the assistance of Dr Ashita Tolwani and Dr Javier A. Neyra for their willingness to share published and unpublished educational materials for this review. Dr Teixeira additionally acknowledges Drs Tolwani and Neyra for their invaluable mentorship and support. Lastly, the authors thank Dr Michael Reaume for reviewing the manuscript and providing important feedback from the perspective of a nephrology trainee.

**Peer Review:** Received June 26, 2024, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form September 24, 2024.