Management of Intermittent Hemodialysis in the Critically Ill Patient

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Abstract
Intermittent hemodialysis remains a cornerstone of extracorporeal KRT in the intensive care unit, either as a first-line therapy for AKI or a second-line therapy when patients transition from a continuous or prolonged intermittent therapy. Intermittent hemodialysis is usually provided 3 days per week in this setting on the basis that no clinical benefits have been demonstrated with more frequent hemodialysis. This should not detract from the importance of continually assessing and refining the hemodialysis prescription (including the need for extra treatments) according to dynamic changes in extracellular volume and other parameters, and ensuring that an adequate dose of hemodialysis is being delivered to the patient. Compared with other KRT modalities, the cardinal challenge encountered during intermittent hemodialysis is hemodynamic instability. This phenomenon occurs when reductions in intravascular volume, as a consequence of ultrafiltration and/or osmotic shifts, outpace compensatory plasma refilling from the extravascular space. Myocardial stunning, triggered by intermittent hemodialysis, and independent of ultrafiltration, may also contribute. The hemodynamic effect of intermittent hemodialysis is likely magnified in patients who are critically ill due to an inability to mount sufficient compensatory physiologic responses in the context of multiorgan dysfunction. Of the many interventions that have undergone testing to mitigate hemodynamic instability related to KRT, the best evidence exists for cooling the dialysate and raising the dialysate sodium concentration. Unfortunately, the evidence supporting routine use of these and other interventions is weak owing to poor study quality and limited sample sizes. Intermittent hemodialysis will continue to be an important and commonly used KRT modality for AKI in patients with critical illness, especially in jurisdictions where resources are limited. There is an urgent need to harmonize the definition of hemodynamic instability related to KRT in clinical trials and robustly test strategies to combat it in this vulnerable patient population.

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Introduction
Intermittent hemodialysis (HD) is the original extracorporeal KRT. It has been used in intensive care units (ICUs) since their initial development in the 1970s to save the lives of countless patients who are critically ill with severe AKI (1). The fluctuations in BP experienced during intermittent HD can be a significant challenge in this patient population. The subsequent development of continuous KRT (CKRT) and prolonged intermittent KRT (PIKRT) has meant that, at many tertiary medical centers, particularly in high-income countries, intermittent HD is no longer the initial KRT modality of choice for patients with multiorgan failure and hemodynamic instability. It should be acknowledged that the superiority of any particular extracorporeal modality of KRT for the treatment of patients who are critically ill with respect to survival or kidney recovery after AKI has not been established and remains a matter of debate (2,3), which is the focus of another review in this series. Nonetheless, intermittent HD remains a cornerstone of KRT around the world (including in high-income countries) to treat patients with severe AKI, and also patients with preexisting kidney failure within the context of their critical illness (4,5). It is therefore essential for clinicians at all stages of training to develop a knowledge and skill set in the provision of intermittent HD in the critical care environment.

This article reviews important aspects of the management of intermittent HD in patients who are critically ill. These include current evidence regarding vascular access, the optimal dose of intermittent HD prescription, factors that contribute to hemodynamic instability during treatment, and potential strategies to mitigate this instability. Additional information pertinent to KRT modality selection, the role of intermittent HD in the management of intoxications, timing of initiation of intermittent HD for AKI, and volume management with KRT is reviewed elsewhere within the Acute Kidney Injury and Critical Care Nephrology series.

Contemporary Use of Intermittent HD in the ICU
The Intermittent HD Prescription in Patients with Critical Illness
Typically, intermittent HD is prescribed in the ICU as a three times per week treatment of 3–6 hours duration (2), although extra treatments may be required to appropriately manage fluid overload, hyperkalemia, or other acute indications. Blood flow and dialysate flow
rates are significantly higher than for CKRT and PIKRT. The dialyzer filter (1.7–2 m²) is also typically around 2.5 times larger than filters used for CKRT, although additional clearance via hemofiltration does not occur using intermittent HD. Details regarding the usual intermittent HD prescription for patients with critical illness are reported in Table 1. Due to relatively short treatment duration and use of higher blood flow rates than CKRT or PIKRT, most patients do not require systemic anticoagulation. For those that do, unfractionated heparin is generally preferred (versus low molecular weight heparin or other anticoagulants) because it allows for anticoagulation to be reversed, and patients who are critically ill are often at higher risk of bleeding.

Clinical Considerations Related to the Use of Intermittent HD in Patients with Critical Illness

The continued importance of intermittent HD in the critical care setting was demonstrated by Hoste and colleagues (4), who prospectively studied 1802 patients at 97 centers in 33 countries during their first week of an ICU admission. Sepsis and hypovolemia were the most frequently reported causes of AKI in this cohort. Participants treated with KRT for AKI (n=243; 14%) underwent 818 KRT sessions, of which 197 (24%) were provided as intermittent HD, 615 (75%) as CKRT, and six (0.7%) as peritoneal dialysis.

The choice of initial KRT modality for a patient who is critically ill depends largely on local resources (i.e., the availability of, and experience with, particular KRT modalities) and, typically, also considers a patient’s hemodynamic status and issues related to vascular access and anticoagulation (3). Figure 1 details patient- and system-level considerations relevant to the delivery of intermittent HD in patients with critical illness.

Given the widespread availability of intermittent HD in both high- and low-income countries, and its relatively lower cost compared with CKRT, intermittent HD is often the default KRT modality for patients who are hemodynamically stable in the ICU. Intermittent HD is also used at many centers for patients who are hemodynamically unstable, where it may be the only available form of extracorporeal KRT. In centers with access to CKRT and/or PIKRT for patients who are hemodynamically unstable, intermittent HD may sometimes be preferred because it affords more rapid clearance of toxins and small solutes (e.g., in the setting of severe hyperkalemia or acidosis, ongoing severe tumor lysis, or an intoxication). In this situation, the higher theoretic risk of exacerbating hemodynamic instability may be outweighed by the benefit to the patient from rapid removal of the toxin or prompt reversal of an electrolyte or acid-base abnormality.

In the absence of a clear indication for intermittent HD, clinical judgment is required to select the appropriate KRT for each individual patient. Criteria for KRT modality selection are often extrapolated from the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN) Study assessing dose of KRT for AKI (6). In this trial, intermittent HD was used in patients with a Cardiovascular Sequential Organ Failure Assessment (CV-SOFA) score between zero and two (7). Essentially, patients did not receive treatment with intermittent HD if they were receiving vaspressors at any dose. Participants still received intermittent HD if there was evidence of hypotension (i.e., mean arterial pressure <70 mm Hg) and/or they were receiving inotropes. Because patients often transition between modalities due to their hemodynamic status, the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI acknowledge that CKRT and intermittent KRT should be used as “complementary therapies” for patients with AKI (3).

Table 1. The intermittent hemodialysis prescription in patients who are critically ill

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Usual Prescription</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>3–6 h, or as tolerated</td>
<td>Longer duration of treatment may reduce hemodynamic instability</td>
</tr>
<tr>
<td>Frequency</td>
<td>Minimum 3x/wk ensuring minimum dose is met (i.e., URR ≥67%)</td>
<td>Extra treatments often required to ensure adequacy, electrolyte, acid-base, and volume status control achieved</td>
</tr>
<tr>
<td>Blood flow</td>
<td>200–500 ml/min</td>
<td>Lower rates used to reduce efficiency for patients at high risk of dialysis disequilibrium syndrome (e.g., first treatment for AKI superimposed on advanced CKD with very high urea)</td>
</tr>
<tr>
<td>Dialysate flow</td>
<td>500–800 ml/min</td>
<td>Lower temperature (i.e., 35–35.5°C) preferred to potentially mitigate hemodynamic instability</td>
</tr>
<tr>
<td>Temperature</td>
<td>35°C–37°C</td>
<td>Primarily diffusive clearance occurs across the filter</td>
</tr>
<tr>
<td>Filter size</td>
<td>1.5–2.5 m²</td>
<td>Consider use of isolated ultrafiltration for a portion of treatment if primary indication for intermittent hemodialysis is volume overload</td>
</tr>
<tr>
<td>Ultrafiltration rate</td>
<td>0–5000 ml/3–4 h</td>
<td>Usually requires hemodialysis nurse and/or hemodialysis technician and portable reverse osmosis machine</td>
</tr>
<tr>
<td>Timing of delivery</td>
<td>Usually during daytime hours</td>
<td>Usually requires hemodialysis nurse and/or hemodialysis technician and portable reverse osmosis machine</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Not usually required</td>
<td>If anticoagulation is required, unfractionated heparin is preferred</td>
</tr>
<tr>
<td>Dialysate [Na⁺]</td>
<td>Approximately 140–150 mmol/L</td>
<td>Higher dialysate [Na⁺] may mitigate hemodynamic instability; avoid in patients with hypernatremia</td>
</tr>
<tr>
<td>Dialysate [Ca²⁺]</td>
<td>1.25–1.75 mmol/L</td>
<td>Higher dialysate [Ca²⁺] may mitigate hemodynamic instability; avoid in patients with hypercalcemia, hyperphosphatemia</td>
</tr>
</tbody>
</table>

URR, urea reduction ratio; [Na⁺], sodium concentration; [Ca²⁺], calcium concentration.

Vascular Access for Intermittent HD in Patients Who Are Critically Ill

Well-functioning vascular access is required to deliver intermittent HD. Table 2 details considerations related to
vascular access selection for patients with critical illness who require intermittent HD. Patients with functional arteriovenous fistulas, arteriovenous grafts, or tunneled HD catheters may undergo intermittent HD using those forms of vascular access. Most patients with AKI require insertion of a temporary, nontunneled HD catheter. Multiple factors should be taken into consideration when choosing the optimal site for nontunneled HD catheter insertion in patients who are critically ill. KDIGO guidelines suggest that the order that insertion sites should be favored in the absence of another indication is: (1) right internal jugular vein, (2) femoral vein (right or left), (3) left internal jugular vein, or (4) subclavian vein (with preference for the dominant side) (3). Although past studies showed higher rates of infection at the femoral site (8,9), the Cathedia trial (n=5,750 patients who were bed-bound with critical illness and required acute KRT) showed similar rates of catheter colonization (a proxy for central line–associated bloodstream infections) at the femoral and internal jugular sites (10), but more catheter dysfunction at the left internal jugular site (11). A prespecified analysis found that the rate of catheter colonization was lower at the internal jugular sites for those with body mass index $<28.4$ kg/m² and lower at the femoral sites for those with a body mass index $<24.2$ kg/m² (10). The subclavian vein is generally viewed as a last choice for nontunneled HD catheter insertion because it may be associated with a higher risk of central venous stenosis (12).

For internal jugular vein catheters, the catheter tip should be positioned at the junction of the superior vena cava and the right atrium (13). Because the anatomy varies, different lengths of nontunneled HD catheter are required according to the position they are placed (see Table 2).

Although KDIGO recommendations do not suggest the use of tunneled catheters for patients with AKI, several observational studies have suggested lower risks of infection and thrombosis, and higher blood flow rates, with the use of tunneled HD catheters (14). More study is needed to determine the feasibility and outcomes of implementing a “tunneled HD catheter first” approach (14). When feasible and safe, tunneled HD catheter insertion should be considered over nontunneled HD catheter insertion if the need for intermittent HD is expected to be prolonged (3,15).

**Dose/Intensity of Intermittent HD for AKI**

Multiple small studies initially suggested a lower risk of death with high-intensity KRT (16). In a single-center, randomized controlled trial that included 160 patients who were critically ill, Schiff et al. (17) assessed whether ICU patients with AKI undergoing daily intermittent HD had different outcomes compared with those treated on alternate days only. The daily intermittent HD arm had an average weekly Kt/V of 5.8 compared with 3.0 for the alternate-day arm. Lower mortality out to 14 days after the
An important issue for evaluating dialysis adequacy is that calculation of the weekly Kt/V requires an estimation of the volume of urea. Given the complex course of many patients in the ICU, their range of comorbidities, the nature of their critical illness, and the interventions used to treat them, there are wide variations in baseline urea values, rates of urea generation, and volumes of distribution in this population (25). These caveats aside, ongoing assessment is needed to ensure that the targeted dose of KRT delivered during those sessions is being achieved.

A secondary analysis from the ATN trial demonstrated that, at the level of a single treatment, there is a strong correlation between the urea reduction ratio and the single-pool Kt/V (26). The authors concluded that targeting a urea reduction ratio of ≥0.67 can provide a simplified means of ensuring that adequate clearance is being achieved for patients with AKI treated with intermittent HD. Beyond ensuring that the minimum dose of intermittent HD is actually delivered, careful longitudinal assessment is required to determine if extra treatments are needed to maintain homeostasis with respect to electrolytes, acid-base parameters, and extracellular fluid volume status (25).

The KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury provides several recommendations for dosing of intermittent HD for AKI (3). Clinicians are advised to prescribe a dose of KRT to be delivered before each session (5.8.1, not graded), with frequent assessment of the actual delivered dose to adjust the prescription (5.8.1, 1B recommendation). The recommended dose is a weekly Kt/V of 3.9 per week (5.8.3, 1A recommendation), which is largely derived from the ATN Study and the Hemodialysis study in patients on maintenance HD (22). This dose recommendation was determined on the basis of the arithmetic sum of the dose per individual treatment under the assumption that a single-pool Kt/V of 1.3 three times per week is equivalent to a single-pool Kt/V of 0.65 six times a week; however, kinetic modeling studies suggest these are not equivalent (23,24) and this recommendation should be taken with some caution.

Vascular Access Options for Intermittent HD

Table 2. Vascular access options for intermittent hemodialysis in patients who are critically ill with AKI

<table>
<thead>
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<th>Vascular Access</th>
<th>Usual Length</th>
<th>Factors in Favor of Insertion/Use</th>
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<tr>
<td>Non-tunneled (temporary) hemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>catheter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right internal jugular site</td>
<td>15–20 cm</td>
<td>Bed-bound with BMI &gt;28 kg/m²; postoperative abdominal aortic aneurysm repair; ambulatory patient/mobility required for rehabilitation</td>
</tr>
<tr>
<td>Femoral sites</td>
<td>20–24 cm</td>
<td>Bed-bound with BMI &lt;24 kg/m²; tracheostomy present or planned soon; emergency HD required plus inexperienced operator and/or no access to ultrasound guidance</td>
</tr>
<tr>
<td>Left internal jugular site</td>
<td>&gt;24 cm (aim for tip to be as close to IVC as possible)</td>
<td>Contraindications to right internal jugular and femoral sites</td>
</tr>
<tr>
<td>Subclavian sites</td>
<td>Approximately 15 cm</td>
<td>Contraindications to internal jugular and femoral sites; right side is preferred</td>
</tr>
<tr>
<td>Tunneled hemodialysis catheter</td>
<td></td>
<td>Prolonged HD is likely to be required (e.g., very advanced CKD at baseline); no significant coagulopathy/anticoagulation; HD not required emergently</td>
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BMI, body mass index; HD, hemodialysis; IVC, inferior vena cava.
*aDepends on patient size. 

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last HD treatment received was found in the daily intermittent HD arm (28% versus 46%; P<0.01) along with faster recovery of kidney function to dialysis independence (9 days versus 16 days; P<0.001). The alternate-day group ultimately received a very low dose of dialysis relative to recommendations established for maintenance intermittent HD (i.e., weekly Kt/V of 3.6) (18,19). In keeping with this, a higher burden of uremic complications was observed in the alternate-day group, including altered mental status, gastrointestinal bleeding, and infection.

The subsequent publication of the Randomized Evaluation of Normal versus Augmented Level (RENAI) (20) and ATN trials (6) definitively established that there is no benefit to higher-dose KRT relative to the minimum doses achieved in those trials. Of those two landmark studies, only the ATN trial included patients treated with intermittent HD. This was a multicenter, open-label, parallel-group, randomized controlled trial of 1124 patients randomized to a strategy of standard-dose versus high-dose KRT. The KRT modality used for patients in both arms was determined according to the CV-SOFA score, as described above. For intermittent HD treatments, the standard-dose arm consisted of three times per week treatments versus six times per week treatments in the high-dose arm. In both arms, the achieved average single-pool Kt/V was approximately 1.1 for initial treatments and approximately 1.3 for subsequent treatments (target, 1.2–1.4).

At 60 days, the primary end point of all-cause mortality was not significantly different in the high-dose versus standard-dose groups (54% versus 52%; P=0.47). Similar results were seen for secondary outcomes, and adverse event rates were similar, although more episodes of hypotension occurred in the high-dose KRT group. In a potentially related finding, a post hoc analysis of the ATN Study, specifically assessing the 246 patients treated only with intermittent HD, found the high-dose group had lower likelihood of recovery to dialysis independence at day 28 (odds ratio [OR], 0.49; 95% confidence interval [95% CI], 0.28 to 0.87) (21).
Hemodynamic Instability during Intermittent HD
Definition, Incidence, and Consequences

Intradialytic hypotension is a commonly encountered problem in patients receiving maintenance HD (27). In that setting, intradialytic hypotension is defined by the National Kidney Foundation Disease Outcome Quality Initiative (K/DOQI) as a decrease in systolic BP ≥20 mm Hg or a decrease in mean arterial pressure ≥10 mm Hg that is associated with symptoms including sighing, yawning, nausea, vomiting, restlessness, dizziness/fainting, or anxiety (28). The applicability of this definition to patients with critical illness is limited (29). First, most patients who are critically ill are unable to report symptoms due to decreased or altered level of consciousness, or the need for sedation and mechanical ventilation. Second, the K/DOQI definition does not account for the possibility of initiation of vasopressors, or an increase in vasopressor dose, during KRT. As such, the broader term “hemodynamic instability related to KRT” may be more applicable to patients who are critically ill and treated with intermittent HD and other forms of KRT in the ICU.

Studies comparing the relative hemodynamic stability afforded by various KRT modalities have used variable definitions for hemodynamic instability related to KRT (30), as have studies evaluating interventions to mitigate its risk (31). This heterogeneity contributes to the wide variation in rates of hemodynamic instability reported across all KRT modalities, including intermittent HD, and represents a substantial challenge to advancing our understanding of its clinical consequences. For intermittent HD, 10%–70% of treatments are complicated by hemodynamic instability according to various definitions used (32).

A recent study by Beaubien-Souligny et al. (33) included 213 patients who were critically ill with AKI transitioning from CKRT to intermittent HD and found that hemodynamic instability occurred in more than half of these patients during their first intermittent HD session. Hemodynamic instability was defined as either discontinuation of intermittent HD for hemodynamic instability, any initiation or increase in vasopressor/inotropic agents, or a nadir systolic BP of <90 mm Hg. The development of hemodynamic instability related to KRT was associated with a significantly higher risk of death (adjusted OR, 2.71; 95% CI, 1.51 to 4.84) (33). The investigators identified a number of independent risk factors for its occurrence, including lower systolic BP before intermittent HD (OR, 0.85 per 10 mm Hg; 95% CI, 0.73 to 1.0 per 10 mm Hg), any vasopressor use (OR, 2.22; 95% CI, 1.11 to 4.43), shorter treatment time (OR, 1.33 per hour; 95% CI, 1.12 to 1.59 per hour), and higher ultrafiltration volumes (OR, 1.26 per percentage of bodyweight; 95% CI, 1.01 to 1.59 per percentage of bodyweight). This strongly suggests that, for patients receiving CKRT with ongoing hypotension or vasopressor dependence, transition to intermittent HD from CKRT should be deferred.

To our knowledge, no clinical trials have yet established a causal link between any particular definition of hemodynamic instability related to KRT and clinically relevant outcomes in patients who are critically ill. Nonetheless, there is much ancillary evidence that hemodynamic instability related to KRT, and the recurrent ischemic insults that result from it, have important clinical consequences. Sequelae of intradialytic hypotension in the maintenance HD population include cardiac arrhythmias, development of fixed myocardial perfusion defects, loss of residual kidney function, brain white-matter changes, intestinal ischemia, seizures, and a higher risk of death (34). It is plausible that recurrent hemodynamic instability related to KRT carries similar risks, which could be magnified in the context of concurrent, severe illness. In patients who are critically ill with AKI, hemodynamic instability related to KRT has been shown to be associated with a higher risk of death (35) and lower likelihood of kidney function recovery (36,37).

Mechanisms for Hemodynamic Instability Related to Intermittent HD

Figure 2 summarizes mechanisms underpinning hemodynamic instability related to KRT (32). In brief, hypovolemia secondary to ultrafiltration and rapid osmotic shifts is believed to be the dominant mechanism for hemodynamic instability related to intermittent HD. If ultrafiltration-and/or osmotic shift–induced reductions in the intravascular volume outpace compensatory plasma refilling by fluid in the extravascular space, the intravascular volume decreases (which also then affects the preload) (38,39). Another mechanism is “myocardial stunning” triggered by intermittent HD, independent of ultrafiltration. This has been demonstrated to occur in both patients on maintenance HD (40) and patients with AKI undergoing intermittent HD (41). If compensatory physiologic responses are inadequate, hemodynamic instability related to KRT results. In patients with critical illness, hemodynamic instability related to KRT may be more frequent because their capacity to mount further compensatory physiologic responses to hypotension (i.e., increased vascular tone and heart rate, recruitment of unstressed blood volume) is often limited. Multiple other patient-related factors can contribute, including baseline cardiac dysfunction, decreased vascular tone from distributive shock, and endothelial disruption during sepsis with multiorgan failure (32).

Because intermittent HD is the KRT modality that is most efficient and, due to its relatively short treatment time, necessitates the highest ultrafiltration rates, it is the KRT modality that will, theoretically, provoke the most hemodynamic instability. Although some centers, largely due to staffing constraints, limit intermittent HD treatment times to 3–5.5 hours, some studies comparing intermittent HD with CKRT used longer treatment times (e.g., 5–5.5 hours) in an effort to mitigate hypotension. In the HEMODIAFE trial (42), which randomized 360 patients who were critically ill with AKI to either intermittent HD or CKRT, the average intermittent HD treatment time was 5.2 hours and the rate of hypotension was similar (complicating 39% versus 35% of treatments, respectively; \( P = 0.47 \)). Performing isolated ultrafiltration during intermittent HD or otherwise lowering its efficiency might also result in better-tolerated treatments (43). Nonetheless, more frequent intermittent HD treatments (with, consequently, less ultrafiltration per treatment and, theoretically, less osmotic shift occurring during successive treatments) has not been shown to mitigate against hemodynamic instability. The ATN Study found that hypotension complicated approximately the same percentage of intermittent HD sessions in both the daily and alternate-day arms (17% versus 18%, respectively),

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thereby resulting in patients in the daily arm undergoing 73% more treatments complicated by hypotension overall (6). This suggests that mechanisms other than hypovolemia due to ultrafiltration and/or osmotic shifts frequently underpin hemodynamic instability related to intermittent HD. As such, myocardial stunning may underpin hemodynamic instability related to intermittent HD in the setting of critical illness to a greater extent than has been recognized historically (41).

Mitigating Hemodynamic Instability Related to Intermittent HD in Patients with Critical Illness

Strategies to mitigate hemodynamic instability related to KRT in patients with critical illness have not been well studied and are largely extrapolated from experience within the maintenance intermittent HD population and small trials specifically in the ICU population. Commonly used strategies to reduce hemodynamic instability during intermittent HD are summarized in Table 3.

A seminal study by Schortgen et al. (50) compared the hemodynamic tolerance of intermittent HD in patients in the ICU before and after the implementation of multimodal, center-specific practice guidelines. Interventions included the use of modified cellulosic membranes, maintaining a dialysate sodium concentration of ≥145 mmol/L, restricting blood flow to a maximum rate of 150 ml/min, ensuring a minimum session duration of 4 hours, and keeping the dialysate temperature at ≤37 °C. Although this important study provided the basis for further work in this area, many of these interventions are now routinely incorporated into modern-day practice.

A 2018 systematic review (31) of trials assessing KRT-related interventions to mitigate hemodynamic instability related to KRT in patients who are critically ill concluded that a combination of sodium profiling alongside other strategies, such as ultrafiltration modeling and cooling the dialysate, might be efficacious. Overall, the body of supporting evidence for this is weak with included studies being small, underpowered, and of low quality, with no definitive evidence that any particular KRT-related intervention reduced the risk of hemodynamic instability. Reduction of dialysate fluid temperature was the focus of a 2006 systematic review comprising 22 studies (n=408 patients, including patients who were hemodynamically “stable” and “unstable”), in which intradialytic hypotension was found to occur significantly more frequently in patients who did not receive cool dialysate (risk ratio, 7.1; 95% CI, 5.3 to 8.9). Post-HD mean arterial pressure was also higher with cool-temperature dialysis by 11.3 mm Hg (95% CI, 7.7 to 15.0); however, all studies were of crossover design and relatively short duration (54).

With respect to novel monitoring techniques, a single-center trial (n=74 patients with AKI; 600 intermittent HD sessions) assessed the use of online blood volume and blood temperature monitoring during treatment (58). This study found that both ultrafiltration profiling and actively controlled body temperature via online monitoring systems (either used independently or simultaneously) had no significant effect on the occurrence of hypotension during treatment (58). Although there has been increased interest in the use of point-of-care ultrasound in the ICU setting, to our knowledge, there is no high-quality data supporting its use in an effort to guide ultrafiltration to avoid hemodynamic instability related to intermittent HD in patients who are critically ill.

Given the strong association of hypoalbuminemia with hemodynamic instability related to KRT, intravenous hyperoncotic albumin has been proposed as a means to reduce
Table 3. Mechanisms for hemodynamic instability related to KRT during intermittent hemodialysis and commonly used mitigation strategies

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Patient-Related and Intermittent HD-Related Causes</th>
<th>Potential Interventions</th>
<th>Rationale for Interventions</th>
<th>Selected Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia/Reduced preload</td>
<td>(1) High ultrafiltration rate</td>
<td>Reduce fluid removal goal; reduce fluid removal rate/longer duration of intermittent HD session; more frequent sessions</td>
<td>Allows for more gradual plasma refilling from interstitium</td>
<td>Lower ultrafiltration rate associated with less hemodynamic instability during first intermittent HD after CKRT (33) More frequent intermittent HD sessions not shown to reduce occurrence of hypotension in the ATN Study (see main text)</td>
</tr>
<tr>
<td></td>
<td>(2) Osmotic shift</td>
<td>Lower blood flow rate Minimize rapid solute shifts and water movement out of the intravascular space</td>
<td></td>
<td>Small trials indicate no difference in BP with varying blood flow rate in maintenance HD (44,45). No trials examined differing blood flow rates in patients with critical illness on intermittent HD (31)</td>
</tr>
<tr>
<td></td>
<td>(3) Impaired plasma refilling rate</td>
<td>Use of isolated ultrafiltration (for part or all of a session)</td>
<td>Minimize rapid solute shifts and water movement out of the intravascular space</td>
<td>Very small trial in patients on maintenance hemodialysis showed isolated ultrafiltration maintained postdialysis orthostatic BP better than standard hemodialysis (43)</td>
</tr>
<tr>
<td></td>
<td>Hypertonic infusions</td>
<td>Hypertonic infused solutions</td>
<td>Minimize rapid solute shifts and promote plasma refilling from interstitium</td>
<td>Limits delivered dose of dialysis markedly</td>
</tr>
<tr>
<td></td>
<td>● Albumin (20%–25%)</td>
<td>Higher dialysate [Na+] and Na⁺ profiling</td>
<td></td>
<td>There is some evidence for hyperoncotic albumin solutions in preventing hypotension and facilitating ultrafiltration, albeit in small trials (46,47), including a recent crossover trial that showed reduction in hemodynamic instability and augmented fluid ultrafiltration with hyperoncotic albumin in patients who were hypoalbuminemic (48)</td>
</tr>
<tr>
<td></td>
<td>● Mannitol</td>
<td></td>
<td></td>
<td>A crossover trial investigating mannitol use in new patients on HD (maintenance HD and AKI) reported some improvement in BP, but overall evidence is inconclusive (49)</td>
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<td>● Hypertonic saline</td>
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<td>Leaky capillary membranes may lead to redistribution of oncotically active substances in critical illness and paradoxically worsen volume overload in the longer term</td>
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<td>Higher dialysate [Na+] and Na⁺ profiling</td>
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<td>High dialysate [Na+] was a feature of a seminal study assessing multiple interventions to prevent hemodynamic instability during intermittent HD, which suggested benefit (50)</td>
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hemodynamic instability related to KRT by increasing oncotic pressure and augmenting vascular refill in response to ultrafiltration (47). A recent crossover trial by Macedo et al. (48) evaluated 65 patients who were hypoalbuminemic (serum albumin <30 g/L) and underwent 249 intermittent HD sessions in hospital (34 sessions were in the ICU). Patients were randomized to receive 100 ml of normal saline or 25% albumin intravenously at initiation of intermittent HD sessions, and the two fluids were alternated for up to six sessions (48). Albumin administration before intermittent HD resulted in fewer episodes of hypotension and allowed for greater fluid removal. This suggests a potential hemodynamic benefit of albumin, but more clinically relevant end points could not be evaluated in this study (48). Hypertonic mannitol has also been assessed as a potential therapy to maintain intravascular filling during intermittent HD and thereby promote better hemodynamic stability during treatment (49), but the overall evidence is similarly limited.

Overall, the best-supported practice for mitigating hemodynamic instability related to intermittent HD in patients who are critically ill are the routine use of low-temperature dialysate and increased dialysate sodium concentration/sodium profiling. The effect of these and any of the other strategies used to mitigate hemodynamic instability during intermittent HD on clinically relevant outcomes remains unknown. If other parameters have been optimized and hemodynamic instability continues to limit achievement of ultrafiltration goals, initiation or uptitration of agents such as the oral α-1 agonist midodrine or intravenous vasopressors are pharmacologic options that can mitigate hemodynamic instability (57). A transition to PIKRT or CKRT could also be considered (these topics are the focus of other reviews in this series).

Conclusions
As the original KRT modality used in ICUs, and the extracorporeal modality with which nephrologists are most familiar, intermittent HD continues to be a mainstay in the
care of patients who are critically ill with severe AKI or preexisting kidney failure. In some patients, regardless of their hemodynamic status, intermittent HD may be the optimal KRT for rapid toxin removal or correction of extreme electrolyte and acid-base derangements.

Although the standard approach to the dialysis prescription is three times per week, clinicians are advised to ensure that the intended dose of each dialysis is actually delivered (urea reduction ratio >0.67 is a reasonable rule of thumb) and to frequently reassess the prescription along with other parameters, including volume status, to determine if extra treatments are required. Hemodynamic instability related to intermittent HD is a frequent occurrence and likely contributes to downstream consequences, including delayed recovery of kidney function and potentially other end organ injury. Our understanding of hemodynamic instability related to KRT is limited, in part, due to substantial heterogeneity in the definition of this condition across various studies. Similarly, the evidence base for strategies to mitigate the risk of hemodynamic instability related to KRT is weak. Despite decades of clinical experience with intermittent HD across a broad mix of patient populations, we have much to learn about how to optimize its utility in patients who are critically ill. Clinical trials with harmonized definitions of hemodynamic instability related to KRT are needed to investigate the roles of different strategies to deliver intermittent HD more safely in the ICU and individualize the approach to treatment.

Disclosures

E. Clark and M. Canney report serving on the editorial board of Canadian Journal of Kidney Health and Disease and being employed by Nephrology Partners of Ottawa. All remaining authors have nothing to disclose.

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Author Contributions

E.G. Clark conceptualized the study and provided supervision; R.J. Chan and W. Helmezi wrote the original draft and were responsible for data curation; and M. Canney, R.J. Chan, and E.G. Clark reviewed and edited the manuscript.

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