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# Management of Acute Kidney Injury in Coronavirus Disease 2019



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**Acute kidney injury is a common complication in hospitalized patients with coronavirus disease 2019. Similar to acute kidney injury associated with other conditions such as sepsis and cardiac surgery, morbidity and mortality are much higher in patients with coronavirus disease 2019 who develop acute kidney injury, especially in the intensive care unit. Management of coronavirus disease 2019-associated acute kidney injury with kidney replacement therapy should follow existing recommendations regarding modality, dose, and timing of initiation. However, patients with coronavirus disease 2019 are very hypercoagulable, and close vigilance to anticoagulation strategies is necessary to prevent circuit clotting. During situations of acute surge, where demand for kidney replacement therapy outweighs supplies, conservative measures have to be implemented to safely delay kidney replacement therapy. A collaborative effort and careful planning is needed to conserve dialysis supplies, to ensure that treatment can be safely delivered to every patient who will benefit for kidney replacement therapy.**

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**Key Words:** Acute kidney injury, COVID-19, Kidney replacement therapy

Acute kidney injury (AKI) is well described in coronavirus disease 2019 (COVID-19) and is associated with high morbidity and mortality. In a large study of 5700 patients in a New York healthcare system, the incidence of AKI in hospitalized patients was 22%, and 3.2% required kidney replacement therapy (KRT).<sup>1</sup> The risk for AKI and need for KRT is significantly higher in critically ill patients with COVID-19, with a correlation between invasive ventilation and initiation of KRT.<sup>2</sup> Data from other studies demonstrated an AKI incidence of 61-76% in the intensive care unit (ICU), with 26-45% of patients in the ICU with COVID-19 needed KRT.<sup>3,4</sup> In this article, we review the management of COVID-19-associated AKI and address the complexities associated with delivery of KRT during a healthcare crisis that strained KRT and other resources across health systems on a global scale.

## NONDIALYTIC MANAGEMENT OF AKI

It is important to note that resources to perform KRT are limited, and dialysis resources were stretched thin during the pandemic. Safe and judicious nondialytic management of AKI is of utmost importance in delaying initiation of KRT, if resources are restricted. In euvolemic patients with AKI stage I or II, a furosemide stress test may help identify those who more likely progress to advanced AKI and need for KRT.<sup>5</sup> However, higher or escalating doses of loop diuretics should be reserved for patients with volume overload, as use of loop diuretics in patients with AKI in general is not associated with decreased need for KRT.<sup>6</sup> In addition, use of diuretics in euvolemic or hypovolemic patients with severe respiratory failure from COVID-19 could lead to exacerbation of the kidney injury, as it is difficult to ascertain their true volume status. If volume resuscitation is required, balanced solutions may be preferred over normal saline in patients at risk for AKI, as 2 recent trials have demonstrated decreased major adverse kidney events and decreased need for KRT with balanced solutions.<sup>7,8</sup> These 2 single-center pragmatic trials compared balanced crystalloids with normal saline for volume resuscitation in the emergency room (SALT-ED trial) and the ICU (SMART trial). In the SALT-ED trial with 13,347 patients, the incidence of major adverse

kidney events with balanced solution was 4.7% vs 5.6% (adjusted odds ratio: 0.82, confidence interval [CI]: 0.70-0.95;  $P = 0.01$ ).<sup>7</sup> In the SMART trial with 15,802 patients, the incidence of major adverse kidney events in the group administered with balanced solutions was 14.3% vs 15.4% in the group that received normal saline (marginal odds ratio: 0.91, 95% confidence interval: 0.84-0.99,  $P = 0.04$ ).<sup>8</sup> This is in contrast to the Saline vs Plasma-Lyte for Intensive Care Fluid Therapy trial that did not demonstrate a reduction in the incidence of AKI with buffered solutions.<sup>9</sup> So, while balanced crystalloids may not be necessary for everyone, it should be considered in patients with hypotension, severe systemic inflammatory response, and elevated serum creatinine on presentation.<sup>10</sup> Regarding metabolic acidosis, the Sodium Bicarbonate to Treat Severe Acidosis in the Critically Ill study demonstrated that administration of intravenous bicarbonate solution in patients with critical illness reduced the need for KRT, when compared with control arm (35% vs 52%, 95% CI:  $-26.4$  to  $-7.0$ ;  $P = 0.0009$ ). The patients receiving bicarbonate infusion also had delayed initiation of KRT (19 days vs 8 days, CI: 3.9-15.6,  $P < 0.0001$ ).<sup>11</sup> At baseline, the patients had severe metabolic acidosis, with a pH of 7.15 and serum bicarbonate level of 13 mmol/L. New potassium binders have become available in the United States over the past few years. Sodium zirconium cyclosilicate has a more rapid onset of action compared with others and has shown to be effective in lowering potassium in multiple setting, including the emergency room.<sup>12</sup> Patiromer is also approved for treatment of hyperkalemia, but the onset of action is prolonged when

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compared with sodium zirconium cyclosilicate (7 hours vs 1 hour) and therefore may not be suitable for immediate correction of hyperkalemia.<sup>13,14</sup> Escalating dosages of intravenous loop diuretics in patients with volume overload, intravenous sodium bicarbonate solution in patients with severe metabolic acidosis, and use of rapid acting potassium binders such as sodium zirconium cyclosilicate for hyperkalemia can potentially delay KRT and conserve valuable resources in the setting of a surge.<sup>5,11,12,15,16</sup>

### KIDNEY REPLACEMENT THERAPY

KRT during acute surge in the hospitals has been extremely challenging, as institutions attempted to balance the provision of appropriately recommended dose of dialysis to individual patients, with conservation of resources to ensure delivery of KRT to every patient. The 4 main considerations in the delivery of KRT during this pandemic should be (1) appropriate and timely KRT for every patient; (2) reduce exposure of personnel to severe acute respiratory syndrome coronavirus 2; (3) conserve personal protective equipment and dialysis consumables; and (4) ensure patient safety. Timing of initiation of KRT in AKI from any etiology is controversial, but multicenter studies in patients with sepsis and other causes did not demonstrate a benefit with early initiation of KRT.<sup>17-19</sup> There are no data to support early initiation of KRT in patients with COVID-19-associated AKI. Initiation of KRT should not be based on stage of AKI but should be considered when life-threatening complications of AKI cannot be managed with conservative measures. Regarding modality of KRT, we followed Kidney Disease Improving Global Outcomes (KDIGO) committee guidelines on choice of initial modality, based on the patient's hemodynamic status.<sup>20</sup> Similarly, the dose of KRT should be based on KDIGO recommendations, with the caveat that a shortage of nursing resources and KRT replacement fluid and dialysate solutions might necessitate reduction in the delivered dose KRT.

### MODALITIES OF KRT

#### Continuous KRT

Continuous KRT (CKRT) is the recommended modality for management of AKI in patients with hemodynamic instability.<sup>20</sup> The KDIGO recommends an effluent flow rate of 20-25 mL/kg/h. Depending on the mechanism of clearance, CKRT can be delivered as continuous venovenous hemofiltration (convective clearance), continuous venovenous hemodialysis (diffusive clearance), and continuous venovenous hemodiafiltration (combination

of both). Convective clearance is not superior to diffusive clearance and, in fact, maybe associated with higher rates of filter clotting owing to higher filtration fraction.<sup>21</sup> We recommend using the available modality at each institution. In the setting of a demand vs resource imbalance because of a surge in patient volumes, consideration should be given to conservation of dialysate and replacement fluids, by reducing flow rates to 15 mL/kg/h, once metabolic control has been achieved.

#### Prolonged Intermittent KRT

Prolonged intermittent KRT (PIKRT) is a hybrid therapy that provides KRT for an extended time but on an intermittent basis.<sup>22</sup> PIKRT can be used as a substitute for CKRT or intermittent hemodialysis (IHD). When hemodialysis machine is used for PIKRT, it is usually referred to as sustained low-efficiency dialysis (SLED). SLED offers the option to use hemodialysis machine to provide KRT to patients who are hemodynamically unstable, and in most institutions that perform SLED, one-on-one hemodialysis nursing is not required. This alleviates the pressure for dialysis nursing support in the times of

an acute surge of patients. SLED is often performed for 8-12 hours, with lower blood and dialysate flow rates. In our, as well as other institutions, CKRT machines that have an effluent drain line are used for PIKRT, as the drain line reduces nursing workload, who otherwise will need to change the effluent bag every 1-2 hours. PIKRT allows 1 CKRT machine to be used for 2-3 patients, depending on the duration of treatment. Provision of PIKRT in this manner al-

lows multiple patients to be treatment with 1 CKRT machine, thereby preventing delays in timely delivery of KRT, which can occur during a surge of patients at individual hospitals, if adequate number of CKRT machines are not available. Another option for PIKRT is to alternate 1 machine between 2 patients every 24 hours.<sup>23</sup>

#### Intermittent Hemodialysis

IHD is the traditional modality for providing KRT in patients who are hemodynamically stable. Based on the Acute Renal Failure Trial Network (ATN) study, the KDIGO and Kidney Disease Outcomes Quality Initiative (KDOQI) recommend provision of IHD 3 times/wk, with a delivered single-pool Kt/Vurea of 1.3 per session.<sup>20,24,25</sup> Providing IHD to a patient with COVID-19 may require one-on-one dialysis nursing support, whether in the ICU or on the general hospital floor. This increases exposure for the nursing staff, and creative maneuvers have been implemented at hospitals to reduce nursing time in the room. Strategies proposed to conserve resources, and decreased exposure includes decreasing

#### CLINICAL SUMMARY

- COVID-19 is associated with a high incidence of AKI.
- Timing, modality, and dose of KRT for patients with COVID-19 associated AKI is similar to other critically ill patients with AKI.
- Hypercoagulability poses a significant problem in patients with COVID-19 and appropriate anticoagulation should be considered for all patients undergoing KRT.
- Providing KRT in the midst of a pandemic poses significant challenges and a coordinated effort is required to manage resources, and to provide treatments in a timely manner to all patients who are deemed appropriate candidates for KRT.

**Table 1. Practice Changes in Delivery of Kidney Replacement Therapy During COVID-19 Pandemic**

Standard Practice	Potential Practice Change in Setting of Surge	Potential Complications with Practice Change
CKRT dosing: effluent flow rate of 20-25 mL/kg/h	In patients who have achieved metabolic control, effluent dosing can be decreased to 15 mL/kg/h to conserve dialysate and replacement fluid	Worsening metabolic control with acidosis and hyperkalemia. Inadequate clearance of medications
CKRT machine set-up: By the bedside in the patient's room	Extension tubing to keep machine outside the room to decrease exposure to healthcare personnel and reduce use of PPE	Hypothermia due to inadequate warming of blood in the return line Disconnections of tubings leading to exsanguination
CKRT solutions: Sterile bicarbonate-based dialysate	Substitute lactate solutions due to shortage of bicarbonate solutions	Lactate solutions may worsen hemodynamic instability. Not suitable in patients with severe shock, liver failure and existing lactic acidosis
CKRT solutions: Sterile bicarbonate-based dialysate	Substitution with bicarbonate solutions in hemodialysis facilities	Solutions do not meet FDA standards to be used as an infusion Can only be used as a dialysate for CVVHD, SLED or for the dialysate component in CVVHDF
PIKRT: used as a substitute for either CKRT or IHD in some institutions	PIKRT was implemented in some institutions to allow on CKRT machine to be used for 2-3 patients	Inadequate clearance Risk for errors with rapid implementation of a new modality at the institution
IHD: Delivered 3 times weekly, with spKt/Vurea of 1.3 per treatment	Decrease treatment time and frequency (i.e. 2 times per week) to optimize resources and decrease exposure	Suboptimal clearance and volume removal, leading to uremic manifestations and volume overload
Peritoneal Dialysis: not usually used in the US in management of adult patients with AKI	Acute PD can be used in case of KRT fluid, machine and filter shortage	Personnel not familiar with placement of PD catheter PD is not suitable for patients who are prone or with high mechanical ventilator needs. Volume regulation is not feasible with PD

CKRT, continuous kidney replacement therapy; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; PD, peritoneal dialysis; PIKRT, prolonged intermittent kidney replacement therapy; PPE, personal protective equipment; SLED, sustained low-efficiency dialysis; spKt/Vurea, single-pool Kt/Vurea.

duration of treatments, decreasing frequency of dialysis to twice a week, and telemonitoring (eg use of baby monitors or tablets to visualize patients from outside the room) (Table 1). Consideration for patient safety should be paramount when implementing any resource conservation and exposure reduction measures. Reducing time and/or frequency of hemodialysis treatments for an extended period can result in uremia and metabolic disturbances, and patients should be carefully monitored for manifestations of inadequate dialysis.

### Peritoneal Dialysis

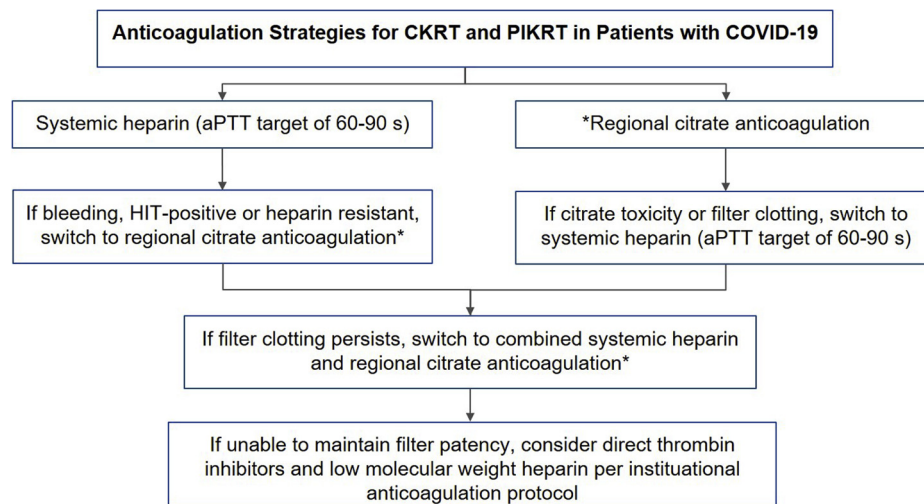
Experiences from resource-limited countries have shown adequate metabolic and fluid control with acute peritoneal dialysis (PD) in AKI.<sup>26,27</sup> Under usual circumstances, acute PD is not used in United States and other developed countries for adult patients with AKI because regulation of ultrafiltration and metabolic control is superior with CKRT in patients who are hemodynamically unstable. However, owing to acute surge during the pandemic in New York, acute PD was implemented in few hospitals because of shortages in extracorporeal KRT consumables, fluids, and nursing.<sup>28</sup>

A bedside catheter placement of a cuffed PD catheter is preferred for patients who are critically ill.<sup>29</sup> Automated

cycler use and extension tubing to keep the machine outside the patient's room can limit exposure to healthcare workers. An average-sized adult can usually tolerate 2-L exchanges; however, reduced volume should be considered for the initial few exchanges to decrease risk of pericatheter leaks. To maximize efficiency of acute PD, an exchange time of 1-2 hours should be used. Assuming a 2-L exchange volume with 60-minute exchange time, ultrafiltration (UF) of about 1.2-3.6 L/d can be achieved with 1.5%, 2.4-7.2 L/d with 2.5%, and 7.2-9.6 L/d with 4.25%. As such, for patients with severe pulmonary edema, initial rapid in-out exchanges using 4.25% can be considered.<sup>29</sup> Theoretically, high-volume PD may impair diaphragmatic movement, increase intra-abdominal pressure, and worsen respiratory mechanics. However, 1 single-center study showed no effect of high-volume PD on pulmonary compliance, although the study excluded patients with  $FiO_2 > 70\%$  and positive end-expiratory pressure (PEEP)  $> 10$  cm  $H_2O$ .<sup>30</sup> In patients requiring prone positioning, PD may not be feasible, but successful delivery has been described in small studies.<sup>31</sup>

### VASCULAR ACCESS FOR KRT

Adequate central venous access is imperative to provide sufficient blood flows during KRT. Hemodialysis catheter length (15-16 cm for right internal jugular [IJ], 19-20 cm for



**Figure 1.** Anticoagulation strategies for kidney replacement therapy in Patients with COVID-19. Abbreviations: aPTT: activated partial thromboplastin time; CKRT, continuous kidney replacement therapy; COVID-19, coronavirus disease 2019; HIT, heparin-induced thrombocytopenia; PIKRT, prolonged intermittent kidney replacement therapy. Ensure appropriate catheter length to reduce risk of clotting. Maintain filtration fraction of  $< 20$ . \*Use citrate anticoagulation only if an existing protocol is available at the institution. Implementation of citrate anticoagulation protocol requires careful advanced planning, and education of physicians and nurses to prevent adverse events. We do not recommend initiation of a new regional citrate anticoagulation during acute surge.

left IJ, 24 cm for femoral) and location must be carefully selected, as inappropriate catheter length can lead to inadequate blood flows that leads to increased filter clotting.<sup>32</sup> The right IJ is the preferred access for KRT as this offers a direct path for the catheter tip to be placed at preferred location – the junction of the superior vena cava and right atrium. There is some controversy whether the second choice should be the left IJ or the femoral vein. The femoral vein site may be associated with higher risk for infections and blood flows may be affected in patients who need to be prone for ventilation. The left IJ can provide inadequate blood flow, especially when shorter catheters are inadvertently placed.<sup>33</sup> In the setting of a surge, physicians not familiar with hemodialysis catheters may be responsible for placing catheters in patients with COVID-19. A cheat sheet with appropriate information related to hemodialysis catheters is a useful tool to distribute in the COVID ICUs. In patients with ESKD, a single-center study has described the use of arteriovenous fistula and arteriovenous graft for CKRT, but this practice is largely limited owing to intricacies with patient monitoring, dialysis and ICU nursing coordination, and risk of extravasation.<sup>34</sup> In patients on extracorporeal membrane oxygenation, unless restricted by high extracorporeal membrane oxygenation flow, CKRT can be performed via the circuit after default CKRT access alarms are reset to accommodate the higher pressures via the extracorporeal membrane oxygenation circuit.<sup>35</sup>

#### HYPERCOAGULABILITY AND KRT

There is growing evidence of endothelial activation causing a hypercoagulable state, leading to higher

incidence of thrombotic complications in patients with COVID-19.<sup>36</sup> In addition to deep vein thrombosis and pulmonary embolism, clotting of extracorporeal circuits is a major concern, as this leads to significant blood loss and excessive loss of KRT filters. Unless there is a contraindication to anticoagulation, we recommend that every patient with COVID-19 starting CKRT or PIKRT receive anticoagulation as per the institution protocol (Fig 1). If initial anticoagulation strategy is not effective, then an alternative plan will need to be implemented. At our center, systemic unfractionated heparin is administered to all patients with COVID-19 on CKRT (target-activated partial thromboplastin time of 60-90 seconds). If patients develop bleeding or other complications from unfractionated heparin, we use regional citrate anticoagulation (RCA), based on our existing policy. In some centers, RCA is the first-line option for anticoagulation for CKRT.<sup>37,38</sup> RCA is a complicated and nursing intensive technique, and we do not recommend hasty implementation of an RCA protocol in the setting of a surge, as this can lead to significant adverse events.<sup>37</sup> Other centers have used other anticoagulation methods such as low-molecular-weight heparin and direct thrombin inhibitors for CKRT. Involvement of pharmacists to establish appropriate anticoagulation protocol is important to ensure adequate dosing and prevent errors.

#### OTHER EXTRACORPOREAL THERAPIES

Hemoperfusion involves nonspecific removal of cytokines by an extracorporeal membrane and has been proposed as a complementary therapeutic option in patients with COVID-19 and multiorgan dysfunction. In the current

crisis, the Food and Drug Administration has granted emergency use authorization to 3 different apheresis and cartridge systems. Hemoadsorption devices have been shown to remove cytokines such as interleukin-6, but this may not translate to improved patient outcomes.<sup>39</sup> The most robust evidence available for use of hemoperfusion in septic shock showed no change in mortality or any other parameter when compared with a sham hemoperfusion group.<sup>40</sup> At this time, we do not recommend use of these devices in the treatment of critically ill patients with COVID-19. However, clinical trials evaluating the effect of these devices and filters on patient outcomes should be considered.

### PROVIDING KRT DURING SURGE

The pandemic and associated surge of patients posed a significant strain on dialysis resources and hospital personnel across the globe.<sup>38</sup> Similar to a patient who requires mechanical ventilation for respiratory failure to sustain life, a patient with AKI or ESKD requires KRT. However, unlike ventilators, there is no national stockpile of KRT machines and filters in the United States. Dialysate and replacement fluids are perishable and cannot be stockpiled. Hospitals had to institute changes to conserve resources and protect personnel (Table 1). Some institutions have resorted to local production of bicarbonate solutions in their hemodialysis facility to overcome shortage of solutions (Johns Hopkins [https://docs.google.com/document/d/17oXLTEqvOtymh\\_aiR8cU39uylud2w\\_QRQCjW2-NXmrA/edit](https://docs.google.com/document/d/17oXLTEqvOtymh_aiR8cU39uylud2w_QRQCjW2-NXmrA/edit) and Cleveland Clinic: <https://consultqd.clevelandclinic.org/an-in-house-solution-to-address-a-national-shortage-of-dialysate-video/>). Hospitals cross-trained other nurses, physicians, and perfusionists to help dialysis and ICU nurses provide KRT in a safe and timely manner. During the surge, institutions implemented various measures such as using extension tubing for CKRT equipment to allow the machine to be kept outside the room. This may have reduced the number of times a nurse had to enter the patient room to troubleshoot machine alarms or to change fluid and effluent bags. However, it should be noted that these extension tubings are not approved by the manufacturers and may increase risk for hypothermia or tubing disconnections resulting in exsanguination. Each institution, along with their nephrology physician and nursing leadership, should establish a plan to provide safe and adequate delivery of KRT in the setting of a surge.

### SUMMARY

Management of patients with COVID-19-associated AKI is generally similar to patients with AKI associated with other etiologies such as sepsis. Conservative management of volume overload, metabolic acidosis, and hyperkalemia can be attempted before considering initiation of KRT. In patients with COVID-19, KRT, especially CKRT and PIKRT, is associated with high rate of circuit clotting, and anticoagulation should be initiated at the start of KRT. Delivery of KRT during a pandemic with acute influx of hospitalized patients poses significant challenges, and

careful planning is required to provide safe and effective KRT to every patient who needs it.

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