Kidney360

Dialysis Filter Life in COVID-19: Early Lessons from the Pandemic

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KIDNEY360 1: 1334–1336, 2020. doi: https://doi.org/10.34067/KID.0006212020

Nephrologists take pride in ensuring that kidney failure is not a life-limiting determinant of health in the intensive care unit (ICU). Although mortality is high in those with AKI, continuous RRT (CRRT) offers a means to support those who require time to recover from their primary insult (1,2). However, for centers hit with early surges from the coronavirus disease 2019 (COVID-19) pandemic, the inability to provide effective dialysis was both a fear and a reality (3,4). Hospitals faced unprecedented supply-chain resource limitations (at least for American medicine) and strains on nursing staff (4). In addition, these patients showed a degree of systemic hypercoagulability that was disproportionate to what was expected in critical illness, with unique features, including a consumptive disseminated intravascular coagulation coexisting with hyperfibrinolysis and increased bleeding risk (5). Maintaining circuit patency, a problem that nephrologists have faced in providing effective clearance and volume management since the origins of hemodialysis, became a common theme once again (3).

A number of studies have documented the efficacy of regional citrate anticoagulation for the prevention of clotting (6), and this strategy has been adopted by many centers, including ours, for the delivery of CRRT in patients with increased clotting risk. It became readily apparent, however, that many patients with COVID-19 had a significant burden of filter clotting, despite the use of regional citrate, optimization of vascular access, and adjustments in the CRRT prescription to reduce intrafilter hemoconcentration. This generated shorter, suboptimal treatments for patients, and caused a higher burden for nurses who had to repeatedly attend to machine alarms inside patients' rooms.

The absence of peer-reviewed literature forced direct communications between colleagues in early COVID-19 "hot spots" and anecdotes from American Society of Nephrology message boards as the only means for early clinical guidance. Many centers trialed diverse strategies, including systemic heparin, heparin in combination with citrate, and direct thrombin inhibitors. The results of these experiences have recently been published (Table 1) (7–9). Shankaranarayanan *et al.* (9) reported their findings from a quaternary care academic institution in New York, including 80 patients and 502 CRRT circuits. The majority of CRRT treatments were done with anticoagulation (70%), a higher usage rate compared with expectations for patients without COVID-19 (10). Relative to no anticoagulation, the risk of clotting was similar in those anticoagulated with citrate (hazard ratio, 0.92; 95% CI, 0.5 to 1.68), and lower in those anticoagulated with systemic heparin (hazard ratio, 0.59; 95% CI, 0.44 to 0.80). The authors noted the surprising efficacy of systemic heparin and argatroban relative to regional citrate alone, but also rightfully pointed out the limitations of this retrospective analysis. Patients that were treated with citrate were often those that had a very high thromboembolic risk, and there was an understandably less-rigorous monitoring of postfilter calcium, which could have influenced the efficacy of the delivered dose of citrate (9). Our group at Mass General Brigham similarly found that, across 65 patients treated with continuous venovenous hemofiltration, the use of systemic heparin was associated with longer filter survival (31 versus 7.5 hours, $P=0.03$) and no difference in a small subgroup comparing citrate with no anticoagulation. A protocol titrating heparin dosing on the basis of anti–factor Xa levels (as opposed to partial thromboplastin time [PTT]) resulted in a longer median filter survival time (7).

In this issue of *Kidney360*, Wen *et al.* (8) provide key peer-reviewed data on filter life in COVID-19. The article describes the filter life of 52 critically ill patients with COVID-19 who required prolonged intermittent RRT *via* sustained, low-efficiency dialysis compared with a control group of patients without COVID-19 in the same center. Similarly to the study by Shankaranarayanan *et al.* (9), they found that treatment with systemic heparin prolonged the duration of dialysis to 12.3 (interquartile range [IQR], 7.2–24.5) hours compared with 4.5 (IQR, 2.5–9.3) hours with citrate or 4.1 (IQR, 2.5–11.3) hours with no anticoagulation. Compared with patients receiving similar CRRT treatments in the pre–COVID-19 era, filter lives were reduced by 50%, and there was a nine-fold increase in the use of heparin, with a corresponding two-fold increase in bleeding complications. There was an inverse correlation between C-reactive protein and filter life, albeit weak ($r=-0.34$), suggesting patients with more systemic inflammation may be at a higher risk for early filter loss. However, this correlation was not seen across other similar measurements of inflammation, such as D-dimer.

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Table 1. Summary of three publications of anticoagulation for continuous RRT in coronavirus disease-19

Study	Population and Outcome	Anticoagulation Strategy (%)	Findings
Shankaranarayanan *et al.* (9)	80 patients (502 circuits) Circuit clotting	No anticoagulation (30)	No anticoagulation: reference
		Citrate (9)[a]	Citrate: HR, 0.92; 95% CI 0.50 to 1.68
		Systemic heparin (50)	Systemic heparin: HR, 0.59; 95% CI, 0.44 to 0.80
		Citrate and heparin (4)	Citrate and heparin: HR, 0.21; 95% CI, 0.08 to 0.54
		Argatroban (7)	Argatroban: HR, 0.29; 95% CI, 0.15 to 0.56
Endres *et al.* (7)	65 patients Time to filter loss	Heparin dosing by anti–factor Xa level (26) versus standard of care (74)[b]	Systemic heparin versus no systemic heparin: 31 (IQR, 5.5–59) h versus 7.5 (IQR, 3.5–31) h (P=0.03)[c]
Wen *et al.* (8)	52 patients (498 circuits)	No anticoagulation (5)	No anticoagulation: 4.1 (IQR, 2.5–11.3) h
	Duration of dialysis session	Citrate (12)	Citrate: 4.5 (IQR, 2.5–9.3) h
		Prefilter heparin (9)	Prefilter heparin: 12.0 (IQR, 3.9–17.0) h
		Systemic heparin (59)	High-intensity heparin: 10.5 (IQR, 5.3–22.0) h
		Citrate and heparin (12)	Heparin and citrate: 12.3 (IQR, 7.2–24.5) h

The percentage of the anticoagulation strategy used refers to the total number of circuits for Shankaranarayanan *et al.* (9) and Wen *et al.* (8), and to the total number of patients for Endres *et al.* (7). HR, hazard ratio; IQR, interquartile range.
[a]54% received additional heparin (4% of total).
[b]Nonrandomized; at the discretion of treating clinician.
[c]This study also analyzed the utility of a heparin titration protocol on the basis of anti–factor Xa levels. Compared with standard of care, the use of anti–factor Xa levels resulted in a longer median third filter survival time (24 [IQR, 15.1–54.2] versus 17.3 [IQR, 9.5–35.1] h; P=0.04).

At this point, there are now three published case series around the use of RRT in COVID-19: this 52-patient cohort from Ochsner Medical Center (New Orleans) (8), an 80-patient cohort from Weill Cornell (New York) (9), and a 65-patient cohort from Mass General Brigham (Boston) (7). These diverse centers demonstrate consistent results: filter life is short in COVID-19 and, although the use of systemic heparin increases filter life and dialysis-treatment duration, filter loss is still higher than in the general ICU literature, where median filter life has been published to be between 20 and 40 hours in clinical trials (6). Although the cumulative experience using citrate anticoagulation was limited in the three studies (only three, 11, and 18 patients, respectively), citrate did not seem to extend filter life—which is surprising, given that citrate outperforms heparin in the general CRRT trial literature (6).

The presumption from these data is that systemic hypercoagulability of COVID-19 leads to decreased filter life from clotting, which is supported by high rates of venous thromboembolism in this population, and the use of systemic heparin results in a longer filter life span (9). Hypercoagulability correlates with inflammation during severe COVID-19 and it has been speculated that systemic heparin might decrease thrombosis of large and small arteries, leading to improved clinical outcomes in some patients who are severely ill (11). However, several unanswered questions remain. First, high levels of circulating cytokines and immense systemic inflammatory response may also be contributing to filter loss. Indeed, Wen *et al.* (8) found that transmembrane pressure, which is a marker of filter clogging, increased more quickly over time in patients with shortened sessions, suggesting that both clotting and clogging may have contributed to filter loss (12). Given the high inflammatory burden of COVID-19, it is plausible that filter clogging in the setting of an increase in cytokines exists, but there is no evidence to date that targeting cytokine removal improves clinical outcomes in patients who are critically ill (13). Second, there is insufficient data to comment whether citrate anticoagulation, or a combination approach using regional citrate and systemic heparin, may be a viable strategy in this population. The risk of bleeding in patients with COVID-19 is high (14), in addition to the burden of close monitoring required for patients on both heparin and citrate. Currently, escalating from regional to systemic anticoagulation must be done at the discretion of the treating nephrologist; additional guidance from clinical trials would be valuable. For now, one must carefully escalate anticoagulation on a case-by-case basis, considering bleeding risk and other potential side effects. Third, many systemic heparin protocols exist, and most dosing schedules are titrated to PTT levels. However, PTT levels are elevated at baseline in severe COVID-19, making them suboptimal markers to target (15). Patients with COVID-19 may also demonstrate some degree of heparin resistance due to their critical illness (16). Serial measurements of other measures of heparin efficacy, such as anti–factor Xa and anti–thrombin III levels, and quantification of proinflammatory cytokines, like IL-6, have all been proposed to quantify risk of filter loss in this population (15). Clinical trials are ongoing to evaluate alternative anticoagulation strategies in the general COVID-19 inpatient population, including assessing higher prophylactic doses and proactive therapeutic approaches (IMPACT Trial,

NCT04406389; COALIZAO ACTION Trial, NCT04394377). We may need to extrapolate some of these results into the CRRT population once they are available.

In conclusion, we thank the authors for sharing their early experience with CRRT and COVID-19. It is vital to accumulate such descriptive analyses to guide our expectations and initial management during this pandemic. In the absence of clear trial data or guideline recommendations, adhering to local standards of care, remaining grounded in evidence-based medicine, and focusing on a harm-reducing RRT strategy remains the foundation for providing care in this crisis. For now, anticoagulation, using some degree of systemic heparin, appears the best approach for patients with severe COVID-19 to maximize our ability to provide effective CRRT. On the positive note, although initial outcomes in resource-stricken areas were concerning, in that the use of CRRT in COVID-19 was associated with a grim prognosis (17), more recent data suggest the overall ICU mortality is similar to that of the non–COVID-19 ICU populations (18). Many of these patients do recover, reflecting the impressive efforts from providers and support staff within our medical infrastructure.

Disclosures

A.S. Allegretti is supported by American Heart Association Award 18CDA34110131 and served on scientific advisory boards for Mallinckrodt Pharmaceuticals. The remaining author has nothing to disclose.

Funding

None.

Acknowledgments

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

A.S. Allegretti and I. Portales-Castillo wrote the original draft and reviewed and edited the manuscript.

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Received: October 16, 2020 **Accepted:** October 28, 2020

See related article, "Dialysis Filter Life, Anticoagulation, and Inflammation in COVID-19 and Acute Kidney Injury," on pages 1426–1431.