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

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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 hemococoncentration. 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), 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.

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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www.kidney360.org Vol 1 December, 2020
These diverse centers demonstrate consistent results: patient cohort from Mass General Brigham (Boston) (7), patient cohort from Weill Cornell (New York) (9), and a 65-patient cohort from Ochsner Medical Center (New Orleans) (8), an 80-patient cohort around the use of RRT in COVID-19: this 52-patient cohort experience using citrate anticoagulation was limited in the trial literature (6).

Systemic heparin might decrease thrombosis of large and small arteries, leading to improved clinical outcomes in some patients who are critically ill (13). 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 PT/PTT levels. However, PT/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,

### 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) Citrate (9)b | No anticoagulation: reference 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 |
| | | Aragrotoban (7) | Aragrotoban: 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 |
| | | Citrate (12) | Citrate: HR, 0.92; 95% CI 0.50 to 1.68 |
| | | Prefilter heparin (9) | Citrate: HR, 0.92; 95% CI 0.50 to 1.68 |
| | | Systemic heparin (59) | Citrate: HR, 0.92; 95% CI 0.50 to 1.68 |
| | | Citrate and heparin (12) | Citrate and heparin: HR, 0.26; 95% CI 0.13 to 0.51 |
| Wen et al. (8) | 52 patients (498 circuits) Duration of dialysis session | No anticoagulation (5) | No anticoagulation: 4.1 (IQR, 2.5–11.3) h |
| | | 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) | Systemic heparin: 12.0 (IQR, 3.9–17.0) 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.

b54% received additional heparin (4% of total).

Nonrandomized; at the discretion of treating clinician.

CThis 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).
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, the use of CRRT in COVID-19 was associated with reducing RRT strategy remains the foundation for providing care in this crisis. This is vital to accurate and reliable patient care. Further, the recent evidence in COVID-19 suggests that the use of CRRT in COVID-19 is associated with a better outcome than no CRRT. However, the use of CRRT should be guided by local guidelines and clinical judgment, considering the potential benefits and risks of anticoagulation.

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.

References

1. Tolwani A: Continuous renal-replacement therapy for acute kidney injury. N Engl J Med 367: 2505–2514, 2012 10.1056/NEnct12060645
2. Allegretti AS, Hunderman G, Chorgarde R, Cosgrove K, Bajwa J, Bhan I: Perspectives of continuous renal replacement therapy in the intensive care unit: A paired survey study of patient, physician, and nurse views. BMC Nephrol 16: 105, 2015 10.1186/s12882-015-0086-5
3. Sise ME, Baggett MW, Shepard JO, Stevens JS, Rhee EP: Case 17-2020: A 68-year-old man with covid-19 and acute kidney injury. N Engl J Med 382: 2147–2156, 2020 10.1056/NEJMcp1020418
4. Reddy YNV, Walensky RP, Mendu ML, Green N, Reddy KP: Estimating shortages in capacity to deliver continuous kidney replacement therapy during the covid-19 pandemic in the United States. Am J Kidney Dis 76: 696–709.e1, 2020 10.1053/j.ajkd.2020.07.005
5. Connors JM, Levy JH: Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost 18: 1559–1561, 2020 10.1111/jth.14849
6. Liu C, Mao Z, Kang H, Ju J, Zhou F: Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: A meta-analysis with trial sequential analysis of randomized controlled trials. Crit Care 20: 144, 2016 10.1186/s13054-016-1299-0
7. Endres P, Rosovsky R, Zhao S, Krinsky S, Percy S, Kamal O, Roberts RJ, Lopez N, Sise ME, Steele DJR, Lundquist AL, Rhee EP, Hibbert KA, Hardin CC, Mcausland FR, Czarnecki PG, Mutter W, Tolkoof-Rubin N, Allegretti AS: Filter clotting with continuous renal replacement therapy in COVID-19 published online ahead of print October 7, 2020. J Thromb Thombolysis 10.1007/s11239-020-02301-6
8. Wen Y, LeDoux JR, Mohamed MM, Ramanan A, Scharwachter M, Dudy L, Lukitsch I, Velez IJCQ: Dialysis filter life, anticoagulation and inflammation in covid-19 and acute kidney injury. Kidney360 1: 1426–1431, 2020
9. Shankaranarayanan D, Muthukumar T, Bhan J, Bhasin A, Gerardine S, Lamba P, Leuprecht L, Neupane SP, Salinas T, Shimonov D, Varma E, Liu F: Anticoagulation strategies and filter life in covid-19 patients receiving continuous renal replacement therapy: A single-center experience [published online ahead of print September 17, 2020]. Clin J Am Soc Nephrol 10.2215/CJN.08430520
10. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P, VA/NH Acute Renal Failure Trial Network: Intensity of renal support in critically ill patients with acute kidney injury [published correction appears in N Engl J Med 361: 2391, 2009]. N Engl J Med 359: 7–20, 2008 10.1056/NEJMoa0802639
11. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z: Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18: 1094–1099, 2020 10.1111/jth.14817
12. Joannidis M, Oudemans-van Straaten HM: Clinical review: The potential of the circuit in continuous renal replacement therapy. Crit Care 11: 218, 2007 10.1186/cc5937
13. Honore PM, Hoste E, Molnar Z, Jacobs R, Joannes-Boyau O, Timsit JF, Abraham E, and the ESPIC Investigators: Where are we and where are we going? Ann Intensive Care 9: 56, 2019 10.1186/s13613-019-0530-y
14. Dorgahaleh A: Bleeding and bleeding risk in covid-19. Semin Hematol 46: 815–818, 2020 10.1055/s-0040-1713434
15. Connors JM, Levy JH: COVID-19 and its implications for thrombosis and anticoagulation. Blood 135: 2033–2040, 2020 10.1182/blood.2020006600
16. Beun R, Kusadasi N, Sikma M, Westerkink J, Huisman A: Anticoagulation strategies and filter life in COVID-19 ICU patients infected with SARS-CoV-2. Int J Lab Hematol 42[Suppl 1]: 19–20, 2020 10.1111/ijl.13230
17. Grasselli G, Greco M, Zanella A, Alboni G, Antonelli M, Bellani G, Bonanomi E, Calvini L, Carlesso E, Castelli G, Cattaneo S, Cerera D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Forti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Moglioli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M; COVID-19 Lombardy ICU Network: Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med 180: 1345–1355, 2020 10.1001/jamainternmed.2020.3539
18. Allegretti AS, Steele DJ, David-Kasdan JA, Bajwa E, Niles JL, Bhan I: Continuous renal replacement therapy outcomes in acute kidney injury and end-stage renal disease: A cohort study. Crit Care 17: R109, 2013 10.1186/cc12780

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.