

COVID-19 and AKI: Where Do We Stand?

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In the year since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, >110 million individuals have been infected and >2.4 million deaths have been attributed to coronavirus disease 2019 (COVID-19) across the world. In the United States, we have seen similarly staggering numbers, with >27 million individuals infected and over 490,000 deaths as of the third week of February 2021. Although predominantly a respiratory infection, COVID-19 often results in multisystem disease, with kidney involvement common in patients with moderate to severe disease. Just as the virus has inundated our health care system, there has been a deluge of publications about SARS-CoV-2 and COVID-19; a search in PubMed returned >100,000 citations, with >800 related to COVID-19 and AKI. Despite this number of publications, it is important to ask what we truly know about kidney involvement in COVID-19 and what still needs to be learned.

Early reports from China described high rates of hematuria and proteinuria but relatively low rates of AKI associated with COVID-19.^{1–3} Highly variable rates of AKI were subsequently reported from Europe and the United States, with some case series describing rates approaching 60% among hospitalized patients.^{4,5} In a recent meta-analysis, the prevalence of AKI among patients hospitalized with COVID-19 was 28%, rising to 46% among critically ill patients, with nearly 20% requiring support with RRT.⁶ Why has there been this high degree of

variability in the reported rates of kidney involvement? One obvious factor relates to the denominator. Because rates have only been reported for hospitalized patients, differences in hospitalization patterns, ranging from hospitalization of all patients identified with infection in some early reports to only the most severely symptomatic patients during the surges in cases triggering latter reports, have likely skewed the data. Even in some of the initial reports from China, rates of AKI in critically ill patients were comparable with those seen in later reports.¹ Data across the broader population of infected patients will be required to understand the true effect of COVID-19 on the kidney. More robust longitudinal data will also be important to understand the effect, if any, of changes in viral strain or improvements in treatment on the frequency and severity of kidney involvement. Early reports from the Department of Veterans Affairs and from New York City have suggested a temporal decline in the incidence of COVID-19–associated AKI.^{7,8} Whether this is related to disease-specific factors, improvements in treatment, or changes to the overall stress on health care systems as the pandemic has surged and eased is unknown.

The etiology of AKI associated with COVID-19 has also been controversial, with considerable debate over whether direct viral involvement of the kidney plays a significant role.^{9–12} Regardless of whether viral involvement of the kidney contributes, in the vast majority of patients AKI is attributable to volume

depletion associated with hyperpyrexia and gastrointestinal involvement or associated with the severe systemic manifestations that cause multiorgan system failure in the most critically ill patients. Although the sheer number of patients with severe AKI has, at times, overwhelmed health care systems during surges in infection,¹³ rates of AKI are strikingly similar to those associated with other forms of sepsis. AKI has been reported in epidemiologic studies from Europe and China in approximately half of critically ill patients with sepsis.^{14,15} In a randomized, controlled trial of resuscitation strategies in severe sepsis and septic shock, AKI was present in approximately half of patients on presentation to the emergency department, and an additional 18.7% subsequently developed AKI during the first week of hospitalization, with two-thirds of patients having stage 2 or 3 AKI.¹⁶ Even among patients with community-acquired pneumonia, approximately one-third develop AKI in the absence of severe sepsis or shock.¹⁷ Thus, although the number of patients with COVID-19–associated AKI has far outstripped the numbers of sepsis-associated AKI seen outside of the pandemic, the rates of AKI are not disproportionate to those seen in other forms of sepsis.

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As in other settings, mortality among patients with COVID-19 complicated by AKI is higher than among infected patients without AKI, with mortality increasing with AKI severity and need for RRT.^{3,4,18,19} Comparison with mortality associated with AKI in other settings cannot be rigorously assessed on the basis of current data, and future analyses will need careful adjustment for overall severity of acute illness. Reported rates of renal recovery have also been variable, with substantial numbers of patients remaining dependent on RRT or with only incomplete recovery of kidney function.^{18,19} A key limitation to our understanding of the long-term consequences of COVID-19–associated AKI is the current absence of systematically collected long-term data on kidney function after hospital discharge.

Whether there are specific and potentially modifiable factors contributing to COVID-19–associated AKI remains to be defined. Included among potential mechanisms are complement dysregulation and hypercoagulable and hyperinflammatory states associated with COVID-19.^{20,21} If targeting these pathways with anticoagulation, glucocorticoids, or specific cytokine inhibitors reduces the risk or severity of AKI remains unknown. In addition, the role of antiviral therapies in prevention and management of AKI is also unknown, particularly as patients with reduced kidney function have been excluded from many clinical trials.^{22,23}

Understanding the pathogenesis of COVID-19–associated AKI will optimally require analysis of kidney tissue. Autopsy studies, although informative, are by nature biased toward the sickest patients and may not reflect the broader range of patients with AKI who survive. Biopsy studies of AKI in general are limited, and there have been only a few reported series of kidney biopsies in COVID-19.^{24–28} These have also been subject to selection bias, with frequent inclusion of patients with atypical features, including heavy proteinuria. As one would expect, the predominant feature associated with AKI is acute tubular injury, with the majority of biopsy series

finding no evidence of direct viral infection of the kidney. Among patients who also have heavy proteinuria, biopsies have demonstrated a variety of pathologic lesions, most notably collapsing glomerulopathy associated with high-risk APOL1 variants.^{25–27,29–31} Ideally, a more systematic approach to biopsies in patients with COVID-19–associated AKI particularly early in the course of disease, including both standard histology and advanced molecular diagnostics, as is being done for non-COVID-19–associated AKI in the Kidney Precision Medicine Project of the National Institute of Diabetes and Digestive and Kidney Diseases would help advance our understanding.³² Unfortunately, the ability to do this may be limited given the constraints imposed by the pandemic. It is also likely that AKI associated with COVID-19 is not a discrete process but rather, a pleomorphic spectrum of injuries and that the nature of injury will differ between patients with AKI on initial hospital presentation and those who develop AKI later in the course of illness.

The management of RRT in patients with COVID-19–associated AKI has posed numerous challenges. Logistically, provision of RRT places nursing staff at increased risk for infection due to prolonged or repeated bedside exposure. Furthermore, during peak surges in cases, shortages of both supplies and trained nursing staff created bottlenecks in providing required treatments.¹³ In addition, anecdotal reports suggest that patients with COVID-19 are more likely to clot their extracorporeal circuit during treatment, requiring intensification of anticoagulant therapy. Although pragmatic decisions have been made to ensure delivery of RRT during surges in the number of patients with COVID-19, including changes to intermittent and continuous therapy protocols¹³ and the use of acute peritoneal dialysis,³³ rigorous evaluation of their safety and effectiveness is needed. Evidence suggesting better outcomes with earlier initiation or higher doses of therapy in COVID-19–associated AKI are lacking. Studies in non-COVID-19 populations have

not demonstrated better outcomes with earlier or higher-dose therapy and have suggested that such strategies are associated with potential delay in recovery of kidney function and prolongation of ventilatory support.^{34–36} The role of novel extracorporeal membranes and adsorption devices for modulation of cytokines, or even removal of viral particles, has not been adequately validated to support routine use in clinical practice.

Finally, it is still too early to understand the effect of the large number of patients with COVID-19–associated AKI on the future epidemiology of kidney disease. It is easy to speculate that unresolved and incompletely resolved AKI will increase the burden of CKD and ESKD and that superimposition of AKI on CKD will accelerate progression to kidney failure. There is a pressing need for systematic follow-up of patients surviving COVID-19–associated AKI to understand its long-term consequences on kidney health.

One year into this pandemic, the importance and vitality of nephrology have been evident. As a discipline, we have provided care to patients with COVID-19–associated AKI under often trying conditions, placing ourselves and our staff at increased risk of infection. Although we have learned much about SARS-CoV-2 and the kidneys, there is still much left to be learned.

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REFERENCES

1. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al.: Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol* 31: 1157–1165, 2020 10.1681/ASN.2020030276
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al.; China Medical Treatment Expert Group for Covid-19: Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 382: 1708–1720, 2020 10.1056/NEJMoa2002032
3. Cheng Y, Luo R, Wang X, Wang K, Zhang N, Zhang M, et al.: The incidence, risk factors, and prognosis of acute kidney injury in adult patients with coronavirus disease 2019. *Clin J Am Soc Nephrol* 15: 1394–1402, 2020 10.2215/CJN.04650420
4. Fisher M, Neugarten J, Bellin E, Yunes M, Stahl L, Johns TS, et al.: AKI in hospitalized patients with and without COVID-19: A comparison study. *J Am Soc Nephrol* 31: 2145–2157, 2020 10.1681/ASN.2020040509
5. Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, et al.: Outcomes for patients with COVID-19 and acute kidney injury: A systematic review and meta-analysis. *Kidney Int Rep* 5: 1149–1160, 2020 10.1016/j.ekir.2020.06.013
6. Silver SA, Beaubien-Souligny W, Shah PS, Harel S, Blum D, Kishibe T, et al.: The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: A systematic review and meta-analysis. *Kidney Med* 3: 83–98.e1, 2021 10.1016/j.xkme.2020.11.008
7. Bowe B, Cai M, Xie Y, Gibson AK, Maddukuri G, Al-Aly Z: Acute kidney injury in a national cohort of hospitalized US Veterans with COVID-19. *Clin J Am Soc Nephrol* 16: 14–25, 2020 10.2215/CJN.09610620
8. Charytan DM, Parnia S, Khatri M, Petrilli CM, Jones S, Benstein J, et al.: Decreasing incidence of AKI in patients with COVID-19 critical illness in New York City [published online ahead of print February 4, 2021]. *Kidney Int Rep* 10.1016/j.ekir.2021.01.036
9. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al.: Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 98: 219–227, 2020 10.1016/j.kint.2020.04.003
10. Puelles VG, Lütgehetmann M, Lindemeyer MT, Sperhake JP, Wong MN, Allweiss L, et al.: Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 383: 590–592, 2020 10.1056/NEJMc2011400
11. Parmar MS: Acute kidney injury associated with COVID-19—cumulative evidence and rationale supporting against direct kidney injury (infection) [published online ahead of print November 5, 2020]. *Nephrology (Carlton)* 10.1111/nep.13814
12. Khan S, Chen L, Yang CR, Raghuram V, Khundmiri SJ, Knepper MA: Does SARS-CoV-2 infect the kidney? *J Am Soc Nephrol* 31: 2746–2748, 2020 10.1681/ASN.2020081229
13. Division of Nephrology, Columbia University Vagelos College of Physicians: Disaster response to the COVID-19 pandemic for patients with kidney disease in New York City. *J Am Soc Nephrol* 31: 1371–1379, 2020 10.1681/ASN.2020040520
14. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al.; Sepsis Occurrence in Acutely Ill Patients Investigators: Sepsis in European intensive care units: Results of the SOAP study. *Crit Care Med* 34: 344–353, 2006 10.1097/01.ccm.0000194725.48928.3a
15. Xu X, Nie S, Liu Z, Chen C, Xu G, Zha Y, et al.: Epidemiology and clinical correlates of AKI in Chinese hospitalized adults. *Clin J Am Soc Nephrol* 10: 1510–1518, 2015 10.2215/CJN.02140215
16. Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, et al.; ProCESS and ProGRESS-AKI Investigators: The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. *Am J Respir Crit Care Med* 193: 281–287, 2016 10.1164/rccm.201505-0995OC
17. Murugan R, Karajala-Subramanyam V, Lee M, Yende S, Kong L, Carter M, et al.; Genetic and Inflammatory Markers of Sepsis (GenIMS) Investigators: Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int* 77: 527–535, 2010 10.1038/ki.2009.502
18. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, et al.; and the STOP-COVID Investigators: AKI treated with renal replacement therapy in critically ill patients with COVID-19. *J Am Soc Nephrol* 32: 161–176, 2021 10.1681/ASN.2020060897
19. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al.; Mount Sinai COVID Informatics Center (MSCIC): AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol* 32: 151–160, 2021 10.1681/ASN.2020050615
20. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogarty AE, Waheed A, et al.: COVID-19 and coagulation: Bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 136: 489–500, 2020 10.1182/blood.2020006520
21. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al.; STOP-COVID Investigators: Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern Med* 180: 1–12, 2020 10.1001/jamainternmed.2020.3596
22. Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, et al.: Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol* 31: 1384–1386, 2020 10.1681/ASN.2020050589
23. Major R, Selvaskandan H, Makkeyah YM, Hull K, Kuverji A, Graham-Brown M: The exclusion of patients with CKD in prospectively registered interventional trials for COVID-19—a rapid review of international registry data. *J Am Soc Nephrol* 31: 2250–2252, 2020 10.1681/ASN.2020060877
24. Sharma P, Uppal NN, Wanchoo R, Shah HH, Yang Y, Parikh R, et al.; Northwell Nephrology COVID-19 Research Consortium: COVID-19-associated kidney injury: A case series of kidney biopsy findings. *J Am Soc Nephrol* 31: 1948–1958, 2020 10.1681/ASN.2020050699
25. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, et al.: Kidney biopsy findings in patients with COVID-19. *J Am Soc Nephrol* 31: 1959–1968, 2020 10.1681/ASN.2020060802
26. Nasr SH, Alexander MP, Cornell LD, Herrera LH, Fidler ME, Said SM, et al.: Kidney biopsy findings in patients with COVID-19, kidney injury, and proteinuria [published online ahead of print November 18, 2020]. *Am J Kidney Dis* 10.1053/j.ajkd.2020.11.002
27. Akilesh S, Nast CC, Yamashita M, Henriksen K, Charu V, Troxell ML, et al.: Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. *Am J Kidney Dis* 77: 82–93.e1, 2021 10.1053/j.ajkd.2020.10.001
28. Rossi GM, Delsante M, Pilato FP, Gnetti L, Gabrielli L, Rossini G, et al.: Kidney biopsy findings in a critically ill COVID-19 patient with dialysis-dependent acute kidney injury: A case against “SARS-CoV-2 nephropathy.” *Kidney Int Rep* 5: 1100–1105, 2020 10.1016/j.ekir.2020.05.005
29. Sharma Y, Nasr SH, Larsen CP, Kemper A, Ormsby AH, Williamson SR: COVID-19-Associated collapsing focal segmental glomerulosclerosis: A report of 2 cases. *Kidney Med* 2: 493–497, 2020 10.1016/j.xkme.2020.05.005
30. Magoon S, Bichu P, Malhotra V, Alhashimi F, Hu Y, Khanna S, et al.: COVID-19-Related glomerulopathy: A report of 2 cases of collapsing focal segmental glomerulosclerosis. *Kidney Med* 2: 488–492, 2020 10.1016/j.xkme.2020.05.004
31. Wu H, Larsen CP, Hernandez-Arroyo CF, Mohamed MMB, Caza T, Sharshir M, et al.: AKI and collapsing glomerulopathy associated with COVID-19 and APOL1 high-risk genotype. *J Am Soc*

- Nephrol* 31: 1688–1695, 2020 10.1681/ASN.2020050558
32. Ong E, Wang LL, Schaub J, O’Toole JF, Steck B, Rosenberg AZ, et al.; Kidney Precision Medicine Project: Modelling kidney disease using ontology: Insights from the kidney precision medicine project. *Nat Rev Nephrol* 16: 686–696, 2020 10.1038/s41581-020-00335-w
33. Sourial MY, Sourial MH, Dalsan R, Graham J, Ross M, Chen W, et al.: Urgent peritoneal dialysis in patients with COVID-19 and acute kidney injury: A single-center experience in a time of crisis in the United States. *Am J Kidney Dis* 76: 401–406, 2020 10.1053/j.ajkd.2020.06.001
34. Bagshaw SM, Wald R, Adhikari NKJ, Bellomo R, da Costa BR, Dreyfuss D, et al.; STARR-T-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group: Timing of initiation of renal-replacement therapy in acute kidney injury [published correction appears in *N Engl J Med* 383: 502, 2020 10.1056/NEJMx200016]. *N Engl J Med* 383: 240–251, 2020 10.1056/NEJMoa2000741
35. Wang Y, Gallagher M, Li Q, Lo S, Cass A, Finfer S, et al.: Renal replacement therapy intensity for acute kidney injury and recovery to dialysis independence: A systematic review and individual patient data meta-analysis. *Nephrol Dial Transplant* 33: 1017–1024, 2018 10.1093/ndt/gfx308
36. Sharma S, Kelly YP, Palevsky PM, Waikar SS: Intensity of renal replacement therapy and duration of mechanical ventilation: Secondary analysis of the acute renal failure trial Network study. *Chest* 158: 1473–1481, 2020 10.1016/j.chest.2020.05.542