

## Kidney diseases in the time of COVID-19: major challenges to patient care

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Viewpoint

COVID-19

The late Colombian Nobel Prize–winning author Gabriel García Márquez wrote “Love in the Time of Cholera,” a complex depiction of the struggle to love during an infectious epidemic (1). In the novel, a rational, responsible physician devoted to science is working to eradicate cholera but is pitted against a passionate, emotional, and impulsive man who wins some of the personal battles. Our current battle against the novel coronavirus 2019 disease (COVID-19) caused by SARS-CoV-2 will require both rational medical science as well as passionate and rapid risk-taking. The current COVID-19 pandemic has affected everyone but presents profound consequences for patients with kidney disease, health care providers, and biomedical researchers. In this Viewpoint, I will discuss a number of kidney-specific aspects of COVID-19 infection, noting therapeutic and basic research opportunities. SARS-CoV-2 entry into kidney epithelial cells via ACE2 Angiotensin-converting enzyme 2 (ACE2) serves as a receptor for SARS-CoV-1 and SARS-CoV-2 (2, 3). ACE2 is expressed in the lung alveolar epithelial cells, oral and nasal mucosa, and other organs, including renal epithelial cells and bladder cells (4, 5). Activation of the renin-angiotensin-aldosterone system is countered by ACE2. SARS-CoV-2 can bind to renal epithelial cells, injure these cells, and subsequently disrupt whole body fluid, acid-base, and electrolyte homeostasis. By injuring kidney epithelial cells, SARS-CoV-2 also disrupts kidney endocrine production of erythropoietin and vitamin [...]

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The late Colombian Nobel Prize-winning author Gabriel García Márquez wrote “Love in the Time of Cholera,” a complex depiction of the struggle to love during an infectious epidemic (1). In the novel, a rational, responsible physician devoted to science is working to eradicate cholera but is pitted against a passionate, emotional, and impulsive man who wins some of the personal battles. Our current battle against the novel coronavirus 2019 disease (COVID-19) caused by SARS-CoV-2 will require both rational medical science as well as passionate and rapid risk-taking. The current COVID-19 pandemic has affected everyone but presents profound consequences for patients with kidney disease, health care providers, and biomedical researchers. In this Viewpoint, I will discuss a number of kidney-specific aspects of COVID-19 infection, noting therapeutic and basic research opportunities.

## SARS-CoV-2 entry into kidney epithelial cells via ACE2

Angiotensin-converting enzyme 2 (ACE2) serves as a receptor for SARS-CoV-1 and SARS-CoV-2 (2, 3). ACE2 is expressed in the lung alveolar epithelial cells, oral and nasal mucosa, and other organs, including renal epithelial cells and bladder cells (4, 5). Activation of the renin-angiotensin-aldosterone system is countered by ACE2. SARS-CoV-2 can bind to renal epithelial cells, injure these cells, and subsequently disrupt whole body fluid, acid-base, and electrolyte homeostasis. By injuring kidney epithelial cells, SARS-CoV-2 also disrupts kidney endocrine production of erythropoietin and vitamin D and impairs blood pressure regulation. Viral entry into renal epithelial cells suggests the possibility that the kidney could also become a viral reservoir once clearance

occurs elsewhere and that urine could be an infectious factor. It will be important to determine if other kidney-resident cells, such as podocytes, interstitial cells, and immune cells, become infected. Given widespread use of ACE inhibitors and angiotensin receptor blockers for hypertension and cardiac and renal diseases, it will also be important to determine whether stopping or adding these drugs is beneficial in acute COVID-19 infections (6). At this point, many medical societies have suggested that the health benefits of ACE inhibitors or angiotensin receptor blockers outweigh potential risks in COVID-19, but this is an important unanswered question.

## COVID-19 and dialysis

Over 500,000 patients in the US are currently on dialysis (7). These patients have depressed immune systems, and those using in-center hemodialysis visit densely populated outpatient units three times per week. Patients on kidney dialysis usually have other comorbidities, such as diabetes, hypertension, and cardiac diseases. Rapid responses to COVID-19 by hemodialysis units, which are experienced in limiting the viral spread of HIV, hepatitis B and C, and other pathogens, will decrease but not prevent its spread. Early in the pandemic, COVID-19-positive symptomatic hemodialysis patients were often transferred to hospitals, both to manage their acute illness and to reduce the risk of spread at their dialysis units. With the spread of COVID-19, dedicated outpatient dialysis units will be needed to care for growing numbers of COVID-19-positive stable hemodialysis patients. Increasing the use of home dialysis with home hemodialysis or peritoneal dialysis, already a goal of the US

Health and Human Services to reduce health care costs and improve health outcomes (8), should be hastened to reduce incidence of COVID-19 infections.

An early Chinese report characterized hemodialysis patients from January 14, 2020, the day the first COVID-19 case was confirmed in the hemodialysis center at Wuhan University, to February 17, 2020. During this period, the authors reported that 37 of 230 hemodialysis patients (16.1%) and 4 of 33 staff members (12.1%) were diagnosed with COVID-19. Six COVID-19-positive patients died within a one-month span in early 2020, but the causes of death may not have been directly linked to COVID-19 (9). Dialysis patients with COVID-19 had less lymphopenia, lower serum levels of inflammatory cytokines, and milder clinical disease than nondialysis patients affected by COVID-19 infection. It is not yet clear whether hemodialysis patients have increased transmissibility/infection rates or worse clinical outcomes. COVID-19 infection leads to systemic inflammation and elevation of D-dimers, protein fragments associated with degradation of fibrin in blood clots. D-dimers can clot dialysis circuits, possibly more often under the conditions of reduced blood flow seen during inpatient continuous dialysis treatments. It will be important to quickly devise plans to keep dialysis patients safe during the COVID-19 pandemic, determine how to best dialyze them, and elucidate the unique relationships between uremia and infection (10).

## COVID-19 and kidney transplantation

Almost all kidney transplant patients are on lifelong immunosuppressive medication, which makes them more susceptible to infections and malignancies. During the early months after transplantation, very high levels of immunosuppression are needed, often with lymphocyte deple-

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tion agents. Patient with donor-specific antibodies and those undergoing rejection need even higher levels of immunosuppression. Initial data about outcomes of long-term stable kidney transplant patients with COVID-19 infections are still emerging, and it is not clear how these outcomes compare with the general population. However, while acutely lifesaving transplants of heart, lung, and high model for end-stage liver disease (MELD) score livers are continuing, most live donor kidney transplantation is currently on hold. Deceased donor kidney transplantation should probably only be performed when lifesaving, such as for a patient running out of vascular access or a highly sensitized patient who may not come across another compatible donor. When deceased donor organs are being accepted in the resource-limited COVID-19 hospital environment, they will most likely be “higher quality” organs, which will recover quickly from storage and ischemic injury, which goes against the current trend of expanding the organ pool (11). Besides the infection concerns for the fresh transplant patient, the effect of elective transplant procedures on hospital resource utilization, diverting care from critically ill patients with COVID-19, is being factored into decisions to reduce kidney transplantation rates. Newer rapid diagnostic techniques are being evaluated to screen deceased donors for COVID-19 at the organ procurement organization before use as well as to screen recipients on or before arrival for the kidney transplant.

There is also a concern that highly immunosuppressed fresh transplant patients can also be infected during the initial hospitalization or in the community after discharge (12). The role of different immunosuppression agents, such as calcineurin inhibitors and intravenous immunoglobulin, in COVID-19 disease is not established. The current pandemic serves as a reminder to try to carefully reduce immunosuppression in stable patients. When a transplant patient becomes infected, early consideration should be given to discontinue antimetabolite immunosuppression, such as mycophenolate mofetil. There will be an increased opportunity for noninvasive biomarkers, such as genomic tools and donor-derived cell-free DNA, to obviate a patient coming to the hospital for a biopsy (13, 14).

## COVID-19 and acute kidney injury

Acute kidney injury (AKI) occurs in about 5% of hospitalized patients and up to 50% of patients in the ICU. The mortality rate from AKI is very high, even in the absence of COVID-19 infections. The published incidence of COVID-19-induced AKI is highly variable to date. An early study from China showed a 27% incidence of AKI in 85 COVID-19-positive patients, as defined by a 30% decrease in glomerular filtration rate (15). There was an increased risk of AKI associated with age >60 years, coexisting hypertension, and coronary artery disease. Six patients had postmortem evaluations that demonstrated severe acute tubular injury, prominent lymphocyte infiltration, detection of viral antigen in tubular epithelial cells, macrophage infiltration, and complement C5b-9 deposition. The lymphocyte and immune cell infiltration found in COVID-19-induced AKI is likely an important pathophysiologic factor in kidney injury and repair (16, 17). In another study conducted on 710 hospitalized patients, 44% of admitted patients had proteinuria, 27% had hematuria, and 3.2% had AKI, and these indicators of kidney impairment were associated with high mortality (18). The associated high mortality from AKI, even with availability of dialysis, could be due to deleterious lung-kidney crosstalk during COVID-19 infection and augmentation of inflammation during AKI (19, 20). Moving forward, use of sensitive AKI biomarkers beyond just evaluating rises in serum creatinine will aid in early detection of AKI or subclinical kidney injury associated with COVID-19 infections (21).

## Future directions

It is important to recognize the unique challenges facing the community of patients with kidney disease during COVID-19 pandemic. These individuals may be at increased risk of infection or worse outcomes and are already experiencing obstacles in their routine medical care. In addition to the tremendous need and opportunity for clinical and basic research into COVID-19 and kidney diseases, local and international collaborations will be more important than ever. Information coming out in bits and pieces will need to be put into systematic registries, and it will

be crucial not to sacrifice scientific rigor in our collective effort to address the new challenges facing patients with kidney diseases in the COVID-19 pandemic.

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