Kidney Medicine Perspective

Acute Kidney Injury and Advanced Kidney Disease in the COVID-19 Pandemic: Proceedings From a National Kidney Foundation Symposium

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The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented and historic public health crisis that continues to expand and evolve. The National Kidney Foundation held a 2-part continuing medical education live virtual symposium on July 16 and July 24, 2020, to address the multiple challenges of COVID-19 in the context of advanced chronic kidney disease. Faculty addressed the pathophysiology, impact, risks, and management of COVID-19 as it relates to advanced kidney disease. Testing, risk mitigation, and inpatient and outpatient management were also addressed. This concise review addresses major findings of the symposium along with certain updates regarding vaccinations since then. These findings include: (1) severe COVID-19 infection has been associated with acute kidney injury, (2) it is essential to prevent and actively manage acute kidney injury to decrease mortality in these critically ill patients, (3) management of patients with advanced kidney disease should be geared toward minimizing their risk for exposure while making sure they are receiving adequate treatments, and (4) patients with kidney disease, especially ones in advanced stages, should be prioritized for vaccination.

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INTRODUCTION

Similar to severe acute respiratory syndrome (SARS) observed during previous coronavirus epidemics, SARS coronavirus 2 (SARS-CoV-2) uses the receptor angiotensin-converting enzyme 2 (ACE2) for cell entry.[1-3] ACE2 is highly represented in lung tissues, which is why certain SARS-CoV-2 are believed to predominantly infect lower airways first. However, coronavirus disease 2019 (COVID-19) is a multisystem disease and can affect the lungs and the heart, brain, liver, and kidney. SARS-CoV-2 can also induce inflammatory cytokine releases, and the resultant "cytokine storm" or "cytokine cascade" is believed to play a major role in organ damage.

Severe COVID-19 infection or mortality can occur in healthy individuals of any age, but it predominantly occurs in adults with advanced age or underlying medical comorbid conditions, including cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer, and chronic kidney disease (CKD).[4-8]

Early reports from China suggested a low incidence of acute kidney injury (AKI; 3%-7%) in hospitalized patients with COVID-19.[9-12] However, these cohorts had a relatively low burden of comorbid illness. More recent data indicate that AKI can occur in more than one-third of patients with COVID-19 infection. For example, a retrospective observational cohort study by Hirsch et al[13] analyzed the data from 5,449 adult patients (median age, 64 years) hospitalized with COVID-19 infection from March 1, 2020, to April 5, 2020, in a New York Health System (13 hospitals). The study showed that AKI occurred in 36.6% of hospitalized patients and was particularly prominent in patients admitted to the intensive care unit or requiring invasive mechanical ventilation.[13] AKI also appears to be associated with higher admission and mortality rates (Fig 1). The median urine specific gravity was high (1.020) and most patients (65.6%) had urinary sodium excretion < 35 mEq/L. Fairly high rates of proteinuria (2-3+ positive in 42.1%) and hematuria (2+ to 3+ positive in 46.1%) were also observed.

Research on the pathophysiology of AKI in patients with COVID-19 is ongoing. Possible risk factors for AKI in patients with COVID-19 infection can include hyper-/hypovolemia, nephrotoxins, secondary infections (ie, sepsis), hypercoagulability, direct SARS-CoV-2 virulence, and the effect of cytokine storm. Primary causes of AKI in COVID-19 include acute tubular injury (acute tubular necrosis), collapsing glomerulopathy, rhabdomyolysis, thrombotic microangiopathy, pauci-immune glomerulonephritis, and kidney infarction.[14-17] The most common pathology appears to be acute tubular injury, whereas the most common glomerular pathology found is collapsing glomerulopathy. Initial studies suggested direct SARS-CoV-2 viral infection in the kidney.[18,19] However, other evidence points to a lack of direct renal invasion due to a possible lack of specificity for some immunohistochemical staining and the possibility that cellular components such as clathrin-coated vesicles or multivesicular bodies may have appeared as viral particles during these initial studies.[20,21]

The presence of underlying CKD has been associated with worse COVID-19 infection, although granular data for different stages of kidney disease are limited. Two studies have found that 13% and 21% of patients hospitalized for severe COVID-19 illness also had underlying CKD at the time of admission, respectively.[22,23] A meta-analysis by Henry et al[24] found that the presence of CKD diagnosis at the time of admission appears to be associated with increased risk for severe COVID-19 infection. A study

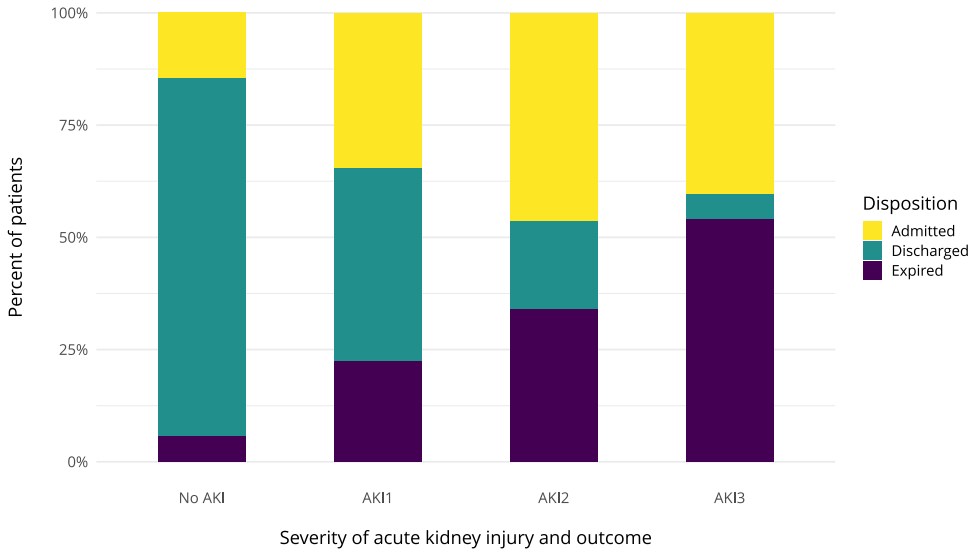

Figure 1. Acute kidney injury (AKI) and outcomes in coronavirus disease 2019. Reproduced from Hirsch et al[13] with permission from Elsevier.

from a New York City hospital system found that patients with CKD and COVID-19 infection had higher risk for mortality.[25] In the study, 6.2% of the 3,391 patients with COVID-19 infection had CKD.

Patients with end-stage kidney disease (ESKD), especially those undergoing maintenance dialysis, are at higher risk for SARS-CoV-2 infection.[26] When infected, patients with ESKD experience exponentially increased risk for severe COVID-19 infection.[26-29] Most recent data suggest mortality rates approximating 20% in patients with ESKD depending on their underlying comorbid conditions or geographic region. Current management recommendations for these patients are similar to those for patients with severe COVID-19 infection and also include antimetabolite reduction for transplant recipients, which centers generally perform albeit based on limited data.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS AND NSAIDS

The use of certain medications in the context of COVID-19 infection has come under scrutiny; however, recommendations regarding the use of renin-angiotensin-aldosterone system (RAAS) inhibitors and avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs) are unchanged in the absence of any compelling data supporting the change in current practices.

Debate continues as to whether patients with COVID-19 infection receiving ACE inhibitors or angiotensin receptor blockers are at increased risk for adverse outcomes.[30-32] Coronaviruses such as COVID-19 bind to their target cells through ACE2, which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessel.[33] However, there is no direct evidence to support an association with these agents specifically, and stopping treatment with these agents in some patients may exacerbate comorbid cardiovascular disease or kidney disease.[30,34] On the basis of current evidence, treatment with RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, being evaluated for, or have COVID-19.

There has been speculation regarding whether NSAID use increases the likelihood of contracting COVID-19 and/or exacerbates symptoms in people with COVID-19 infection. Concern about possible negative effects of NSAIDs was raised by reports about individuals with COVID-19 receiving NSAIDs early in the course of infection and experiencing severe disease.[30,33] There has also been speculation about the possible role as an anti-inflammatory, given that the cytokine storm is believed to cause most of the negative outcomes of COVID-19. Current data show no strong evidence in favor of or disputing the use of NSAIDs with COVID-19 infection. Patients with CKD should be advised to avoid NSAIDs because they can negatively affect kidney function.[35]

MANAGEMENT OF AKI IN COVID-19

It is essential to prevent and actively manage AKI in critically ill patients with COVID-19 infection to help decrease mortality. Supportive and critical care strategies should include adjustment of fluid balance according to volume responsiveness, hemodynamic monitoring in patients with kidney involvement, avoidance of nephrotoxins, and treatment of secondary infections and sepsis.[36] Volutrauma and barotrauma could be mitigated through the application of lung-protective ventilation, which may also lower the risk for AKI by limiting ventilation-induced hemodynamic effects. Volutrauma refers to lung injury due to overdistention during mechanical ventilation, whereas

barotrauma refers to physical damage to body tissues caused by a difference in pressure between a gas space inside and the surrounding fluid.[37] Early and aggressive anticoagulation and efforts to inhibit cytokine release syndrome should also be considered when appropriate.[38]

Aggressive extracorporeal ultrafiltration may precipitate or worsen hypotension among patients with COVID-19 infection with marked hemodynamic instability and/or refractory fluid overload.[39,40] In these situations, initial support with continuous kidney replacement therapy (CKRT) can offer more consistency in ultrafiltration, greater hemodynamic tolerance, and less metabolic and osmotic fluctuations.[39] Patients with COVID-19 infection require frequent mobilization and pronation; therefore, alternative therapies, such as prolonged intermittent KRT, slow low-efficiency dialysis, and slow continuous ultrafiltration, represent a reasonable compromise between continuous and intermittent modalities.[39] Prolonged intermittent KRT can be considered as an alternative to CKRT if there is not sufficient equipment to meet demand.[41] Peritoneal dialysis has also been used in patients with COVID-19 and AKI during periods of increased demand.[38,42]

Indication for CKRT can include oliguria with refractory hypovolemia, hyperkalemia, severe acidosis, and azotemia. Medium- or high-cutoff dialyzers, or hemadsorption devices for special cases, can be considered.[39,43-45] It is also important to ensure the availability of CKRT machines and additional supplies, intensive care unit staff, special membranes, or sorbent cartridges, especially in an area of high COVID-19 incidence. Comprehensive monitoring of CKRT in critically ill patients with COVID-19 includes catheter position (after pronation), circuit patency (pressures), fluid balance, hemodynamics, and delivered dialysate/filtrate/effluent rate. Approaches to management may evolve as additional studies and evidence become available.

Emerging Therapies in AKI From COVID-19

Severely ill patients with COVID-19 infection are at elevated risk for multiorgan dysfunction due to cytokine release syndrome. Increased levels of interleukin 2 (IL-2), IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor, interferon gamma, and tumor necrosis factor have all been identified.[38] A dysregulated host response to infection can lead to multisystem organ failure. This process can depend on systemic inflammation from innate immunity and possibly severe immunosuppression from adaptive immunity. Therapies such as interferon gamma inhibitors, corticosteroids, intravenous immunoglobulin G, tumor necrosis factor blockers, and tocilizumab have been postulated to be beneficial in the treatment of cytokine storm.[38] Modalities that may aid cytokine removal or modulation include cascade hemofiltration, (high volume hemofiltration), high-adsorption hemofiltration, plasmapheresis, hemoperfusion, and high-cutoff/medium-cutoff membranes.[43] The aim of these interventions is to modify the cytokine to chemokine ratio from the tissues to the blood and/or decrease the peaks of cytokine concentrations.

The removal of cytokines through extracorporeal therapies has been an active area of study.[43,45,46] Extracorporeal treatments should theoretically not interfere with experimental antibody-based therapies used in COVID-19 (eg, tocilizumab, convalescent plasma, and intravenous immunoglobulin Gs) because hemodialysis filters and hemadsorption cartridges do not remove antibodies. The size of these antibodies exceeds the size of molecules that can be removed with extracorporeal treatments. Studies indicate that certain filters can remove inflammatory markers in critically ill patients with COVID-19 infection.[43,45,46] However, further research is necessary to explain the outcomes related to these therapies.

Other therapies, such as hydroxychloroquine, vitamins, selenium, zinc, and pyrithione, have been proposed as treatments but all lack substantial evidence for use in patients to treat COVID-19, including those with advanced kidney disease.[47]

Remdesivir has been approved for severe symptoms in hospitalized patients with COVID-19. The use of remdesivir in the context of AKI in COVID-19 has been an area of research. Patients with advanced kidney disease were not included in remdesivir trials due to concerns about the drug's potential toxicity among these patients. These concerns relate to remdesivir's actions and the potential accumulation of its sulfobutylether-beta-cyclodextrin (SBECD) carrier. However, remdesivir has a limited duration of treatment (5-10 days) and a relatively low concentration of SBECD carrier. Therefore, the benefits may outweigh the risk in select patients with COVID-19 infection with estimated glomerular filtration rates < 30 mL/min/1.73 m^2.[48]

COVID-19 TESTING AND RISK MITIGATION IN DIALYSIS FACILITIES

Patients with advanced kidney disease, such as those with ESKD, are at increased risk for SARS-CoV-2 infection and complications of COVID-19 due to multiple risk factors, including older age, comorbid conditions (eg, cardiovascular disease, hypertension, diabetes, and chronic lung disease), and an underlying immune-compromised state. Patients receiving maintenance dialysis are at high risk for SARS-CoV-2 exposure because of their obligation to congregate frequently for prolonged periods with other patients, dialysis staff, and transportation providers.[49] Patients with advanced kidney disease are also more likely than the general population to reside in skilled nursing facilities and have higher rates of hospitalization and physician visits, further increasing risk for exposure.

Early reports on the prevalence and outcomes of SARS-CoV-2 infection in maintenance dialysis patients from Wuhan, China, indicated low infection and mortality rates.

However, Xiong et al[50] conducted a retrospective study of 65 centers in Wuhan, China, and found a 2.1% incidence rate of COVID-19 among maintenance hemodialysis patients and a mortality rate of 31%. Only ~50% of patients manifested fever, whereas ~20% of infected patients were asymptomatic. Studies from Europe also indicate high mortality among hemodialysis patients with COVID-19.[51,52] Data from ERACODA (ERA-EDTA COVID-19 database for patients receiving dialysis or living with a kidney transplant) indicate that mortality in transplant recipients is 18% and in dialysis patients is 20%.[53] A study using data from OpenSAFELY also found lower transmission rates but high fatality among dialysis patients compared with the general population.[54]

The diagnosis of an acute infection cannot be definitively made without microbiological testing (reverse-transcriptase polymerase chain reaction). However, testing all patients has been hampered by a limited test capacity and shortages in reagents and other testing supplies. High-priority individuals have been suggested to include symptomatic health care workers, symptomatic people who have known risk factors for severe COVID-19 illness, and hospitalized patients (in particular those who are critically ill with respiratory illness).[55] Despite their high risk for COVID-19 infection, patients with ESKD are not designated as a mandatory screening cohort.

Antibodies most commonly become detectable 1 to 3 weeks after symptom onset. Therefore, it is possible for a person to have a positive viral testing result and a negative antibody testing result. Currently, there is no identified advantage of assays whether they test for IgG, IgM, and IgG or total antibody.[55] Antibody testing has not been standardized and availability for large dialysis organizations is limited.

Recommendations on the prevention and control of COVID-19 among patients receiving maintenance dialysis are available.[49,56,57] Possible elements of COVID-19 risk mitigation within a dialysis facility should include education of patients and health care workers of hand and respiratory hygiene and coughing etiquette and use of personal protective equipment (PPE). Patients should be advised to call ahead of a visit and should be asked if they have symptoms, have traveled to endemic areas, or have had contact with persons infected with COVID-19. Medically stable patients can wait for evaluation in their private vehicle or outside the clinic facility.[49]

All should wear masks and symptomatic individuals should not enter the facility until a plan for isolation and testing is in place. Triage planning should identify patients with fever or symptoms of respiratory infections before they enter the treatment area and should include separate rooms or cohorting of multiple patients, as needed. Hepatitis B isolation rooms should be used only if the patient is hepatitis B positive or there is no other patient in the facility who is hepatitis B positive. If multiple patients are infected, they should be cohorted to separate those with COVID-19 infection from those who are not thought to be infected. Patients should be separated by 6 feet (~2 m) in all directions. Dialysis machines and stations should be disinfected, including all high-touch areas and surfaces postdialysis. A select group of health care workers should also be assigned to patients who have symptoms or illness.[49]

Management of resources and health care staff is also important. Elements can include keeping track of PPE inventory, prioritizing use of PPE to conserve stocks, considering extended use of eye and face protection, considering recycling of PPE, and alternative PPE production methods. The work force should be used efficiently as much as possible, back-up lists should be created, and staff should be cross-trained so that positions can be filled if health care workers become sick.[49] Emotional and mental health check-ins for health care workers are also important.

HOME DIALYSIS AND COVID-19

Management of dialysis patients should be geared toward minimizing their risk for COVID-19 infection while making sure they are receiving adequate and proper treatments. COVID-19 presents a catabolic state and patients should not miss their dialysis sessions to avoid the need for hospitalization from preventable causes such as hyperkalemia and hypervolemia.[42]

Home dialysis offers a way to help minimize the risk for dialysis patient exposure by supporting social distancing, sheltering in place, and reduction of transportation needs. Home dialysis requires most patients to visit the clinic once a month for evaluation, barring any complications. In most cases, the patient or family member performs dialysis, which can also reduce stress on the health care work force. One epidemiologic study from Italy showed that the COVID-19–positive proportion was significantly higher in in-center hemodialysis patients (3.55%) than patients receiving peritoneal dialysis (1.38%).[52]

Multiple strategies can also be applied to help these at-risk patients remain home as much as they can, including using telehealth capabilities (eg, remote monitoring capability and telehealth platform) and drawing monthly laboratory test specimens at home as much as possible.[58] Contracted courier services can deliver monthly medications (eg, for anemia and mineral and bone disease) and collect samples (eg, urine and dialysate to bring back to the unit if necessary).[52]

It is important to manage patients proactively to prevent hospitalization. Periodic clinical evaluations can provide reassurance to patients while giving providers valuable updates on clinical status. Volume status should be closely monitored to reduce the risk for hospitalization. Measurements of routine clearances and membrane function can be suspended in areas of peak COVID-19 cases, as long as symptoms and serum urea nitrogen and potassium levels are adequately controlled.

Incident home patients, those with peritoneal dialysis catheter complications, home hemodialysis patients with

access trouble, and patients deemed unstable cannot avoid in-person visits. All screening measures described should be carried out for these visits as well.[42] Patients who are newly started on peritoneal dialysis or home hemodialysis should preferably have a comprehensive first monthly visit at the clinic.[59] Screening and measures to mitigate COVID-19 risk for dialysis patients should also be performed as described.

VACCINATION

A recent bright spot in the COVID-19 story is the emergency use authorization of 2 COVID-19 vaccines in December 2020. Both vaccines contain messenger RNA that can instruct cells in a person's body to make the SARS-CoV-2 virus's "spike" protein. Copies of the spike protein are then produced by the body's cells, which allows the body to produce an immune response against the virus. There are other vaccines using a modified adenovirus vector to deliver a COVID-19 spike protein to patients or ones using traditional inactivated virus delivery. A modified adenoviral vector vaccine received emergency use authorization in February 2021.

In its most recent meeting, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommended that both health care personnel and long-term care facility residents (phase 1a) should be the first to receive the COVID-19 vaccine.[60] They also recommended that if COVID-19 vaccine supply is limited, persons 75 years and older and frontline essential workers (phase 1b) should be offered vaccination next, followed by persons aged 65 to 74 years, persons aged 16 to 64 years with high-risk medical conditions, and other essential workers (phase 1c). Patients with kidney disease are included in phase 1c despite strong recommendations from multiple advocacy groups for including them in earlier phases for obvious reasons.

It is also notable that patients with ESKD have not been enrolled widely in COVID-19 vaccination trials, if at all. Although limited data from earlier vaccine trials for other infections suggest possible attenuated immune response in patients with ESKD, there are essentially no data to assess the efficacy of the new vaccines to date, and studies exploring the safety and efficacy of COVID-19 vaccines are urgently required in patients with ESKD. However, preliminary data suggest that the antibody response to SARS-CoV-2 (specifically IgG against nucleocapsid and spike antigens) are adequately maintained in most maintenance hemodialysis patients 6 months after initial infection, suggesting a high likelihood of a robust immunogenic response to vaccination in patients with ESKD.[61] Notably, the American Society of Transplantation also recommends vaccination for kidney transplant recipients.[62]

CONCLUSIONS

The COVID-19 pandemic poses multiple health care challenges, including management of both acute kidney disease associated with COVID-19 and COVID-19 infection in patients with underlying CKD. Data to date clearly show that AKI is common in critically ill patients with COVID-19 infection, especially those who require mechanical ventilation. Innovative approaches for KRT may be required in these patients due to concurrent complications such as volume overload and hypercoagulability. Pharmacologic and nonpharmacologic therapies for critically ill patients could be considered complementary, recognizing the possibility that that no single modality could show clear evidence of survival advantage across all patients. Patients with advanced kidney disease tend to have lower transmission rates compared with the general population but in those who are infected, the mortality risk is exponentially increased. The optimal approaches for the care of these patients include continuation of diligent mitigation procedures along with prioritization of vaccination of patients with ESKD and dialysis unit personnel.

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