COVID-19 – A Kidney Perspective

JIE TANG, MD, MPH, MSc, FASN
GUEST EDITOR

The novel coronavirus disease 2019 (COVID-19) outbreak, first reported on December 8, 2019 in Wuhan, China, was designated as a pandemic by the World Health Organization (WHO) on March 11, 2020. This disease, recognized as an infection by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread quickly throughout the world. As of August 23, 2020, over 23 million laboratory-confirmed cases had been documented globally, with more than 800,000 deaths worldwide. The mortality rates vary significantly among studies from 0.3% to 10%, partially reflecting the differences in local policy, access to diagnostic testing, and health care resources and response.

Clinical presentations of COVID-19 can range from asymptomatic infection, self-limited influenza-like symptoms, acute pneumonia to severe respiratory failure. COVID-19 has life-threatening effects far beyond its respiratory manifestations. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptor, which is highly expressed in the kidney, providing a route for direct infection. Coupled with vascular injury and inflammatory insult, acute kidney injury (AKI) has been found in COVID-19 with cumulative incidences ranging from 0.9% to 29%. However, the epidemiology, management, and associated outcomes have varied greatly between studies and the pathophysiology remains unclear.

Besides AKI, there is a paucity of data on the risk factors and outcome of SARS-CoV-2 infected patients with underlying kidney disease, including those receiving dialysis or underwent kidney transplantation. These groups of patients are unique in view of their immunosuppressed status.

The ongoing COVID-19 pandemic carries serious medical, psychosocial, and economic consequences. Understanding its pathophysiology, clinical course, management strategy and therapeutic response are of paramount importance. Here, we will synthesize the current literature on COVID-19 and provide reviews on COVID-19 testing, acute kidney injury, SARS-CoV-2 infection in patients with end-stage kidney disease, and those who received a kidney transplant.

Author Contributions

This issue of the *Rhode Island Medical Journal* features a series of review articles on the nephrology topics related to the COVID-19 pandemic.

Testing for SARS-CoV-2 (COVID-19): A General Review, written by **ERIC W. TANG**, **APRIL M. BOBENCHIK, PhD**, and **SHAOLEI LU, MD, PhD**, will provide an overview of SARS-CoV-2 testing.

COVID-19 and Kidney Injury, written by **MATTHEW LYNCH, MD**, and **JIE TANG, MD, MPH**, will provide a review of current literature on the topic and discuss the pathophysiology of AKI as well as current knowledge gaps.

COVID-19 and ESKD, written by **NATHAN CALABRO-KAILUKAITIS, MD**, and **ANKUR SHAH, MD**, will review COVID-19 disease presentation, management and outcomes in the dialysis patient population.

Kidney Transplantation and COVID-19, written by **BASMA MERHI, MD**, and **REGINALD GOHH, MD**, will review COVID-19 disease presentation, management and outcomes in the kidney transplant patient population.

Guest Editor

Jie Tang, MD, MPH, MSc, FASN, is an academic nephrologist from Brown Physicians, Inc. He is practicing at Lifespan Hospitals, and the Veteran's Administration Medical Center of Providence. He is an Associate Professor of Medicine at the Alpert Medical School of Brown University. His primary research interest is in the areas of chronic kidney disease and kidney stone.

Testing for SARS-CoV-2 (COVID-19): A General Review

ERIC W. TANG; APRIL M. BOBENCHIK, PhD, D(ABMM); SHAOLEI LU, MD, PhD

ABSTRACT

The rampant COVID-19 pandemic has strained the testing capabilities of healthcare centers across the country. Several nucleic acid and serologic assays are available or currently being developed to meet the growing demand for large-scale testing. This review summarizes the developments of commonly used testing methods and their strategic use in clinical diagnosis and epidemiologic surveillance. This review will cover the basic virology of SARS-CoV-2, nucleic acid amplification testing, serology, antigen testing, as well as newer testing methods such as CRISPR-based assays.

KEYWORDS: COVID-19, RT-PCR, serology testing

INTRODUCTION AND VIROLOGY OF SARS-COV-2

In December of 2019, an unknown pneumonia outbreak started in the Wuhan province, later determined to be caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Later named Coronavirus Disease-19 (COVID-19), widespread human-to-human transmission led to over 21.7 million confirmed cases and 775,937 deaths among over 200 countries as of August 17, 2020.[1] The novel disease has and continues to spread rapidly throughout many countries including the United States.

Coronaviruses are separated into four main sub-groups: alpha, beta, gamma, and delta. Only seven alpha and beta coronaviruses are known to infect humans. These are positive-sense single-stranded RNA viruses. Four of the most common types (229E, NL63, OC43, and HKU1) are endemic globally and usually cause mild to moderate upper-respiratory tract illness, accounting for 10–30% of all such infections in adults. Three other coronavirus strains, known as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, are associated with epidemiological outbreaks and have a much higher mortality rate.

SARS-CoV-2 is estimated to have a basic reproduction number (R0) of about 2.5, with a global estimate displaying a 1.2%–13.9% case fatality rate (CFR) at the time of writing.[1] In comparison, SARS-CoV has an R0 value of 3 with a CFR of 15% and MERS-CoV has an R0 value of 1 with a CFR of 35%.[2,3]

These three coronavirus strains have some distinguishing characteristics which account for their increased virulence compared to the endemic coronavirus strains. The spike glycoprotein (S protein) of MERS-CoV binds to cell surface receptor dipeptidyl peptidase 4 (DPP4), while the S protein of SARS-CoV and SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) on their host cells.[4,5] Notably, SARS-CoV-2 displays a 10- to 20-fold greater binding affinity compared to SARS-CoV – a characteristic that is explained by some unique genetic inserts in its spike glycoprotein.[6]

NUCLEIC ACID AMPLIFICATION TESTS (NAATS) OF SARS-COV-2

Overview

Similar to many RNA virus detection assays, SARS-CoV-2 NAATs use reverse transcription-polymerase chain reaction (RT-PCR) to detect viral genomes with high sensitivity and rapid turnaround times. NAATs target conserved regions located in the open reading frame-1ab (ORF1ab) gene as well as the genes of envelope (E), spike (S), and nucleocapsid (N) proteins.[7] NAATs are widely available and remain the primary methods of diagnosing COVID-19 disease.

Specimen Types

Several specimen types have received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA). The most frequently used are the nasopharyngeal (NP) swab, nasal swab, and oral pharyngeal (OP) swab. Recently, saliva-based PCR testing also received FDA EUA approval.

NP swabs are samples collected along the posterior wall of the nasopharynx and are the most appropriate sample type due to the location of the virus within the upper respiratory tract. However, its use is limited due to the requirement of special training in collection technique. Nasal swabs, on the other hand, can be self-collected by the patient, eliminating the need for contact with a healthcare provider. Nevertheless, tests with these samples are subject to a slight decrease in sensitivity due to their suboptimal sample location. OP swabs are directed towards the rear of the oropharynx and are used as an alternative site when an NP or nasal swab cannot be obtained. Saliva is the easiest to obtain and has been gaining popularity in massive testing plans despite claims of such samples having a lower yield. In addition to

upper respiratory tract specimens, lower respiratory tract specimens from bronchoalveolar lavage (BAL) have provided the best yield,[8] but the bronchoscopy procedure is considered to be rather invasive.

Testing Turnaround Time

The turnaround time is the time it takes from collecting a sample to reporting a result. Many factors should be considered, such as location and method of collection, testing method being used, and the location where the test is being performed. The vast majority of the NAATs are performed in an off-site location located away from the patient due to the requirement of high complexity laboratories to perform the NAATs. The exceedingly large volume for diagnosis and screening frequently leads to increased turnaround time in many labs. Where there is a high test volume but a limited number of certified labs, one solution is to use pooled testing.

Pooled testing aims to increase the efficiency of identifying positive cases while minimizing the number of tests needed to screen a population. Pooled testing involves combining several samples into a pool and testing them all at once. If the pool result is negative, all samples included are presumed to be negative. If the pool test is positive, then each sample will be re-tested to identify individual positive samples. Pooled testing takes two steps to identify positives but is efficient when the prevalence of the virus is low because the majority of the samples will be negative. It allows for a great number of individuals to be screened using far fewer testing resources.

Assay Sensitivity and Specificity

Despite having high analytical sensitivity and specificity values, NAATs have a few limitations. Notably, the detectability of the SARS-CoV-2 genome may vary depending on the disease stage. The current consensus is that NAAT assays are the most sensitive during the acute stage of infection. The timing of the test is critical, as testing in the early phase of the incubation period and during the later stages of infection will lead to significant false negatives. When used appropriately, these tests have a very high sensitivity, being able to detect as few as 10–100 copies of viral RNA per milliliter in a sample.[9] They also have a high specificity in that they do not cross-react with other coronaviruses. While these values vary depending on the specific test and manufacturer used, all such assays have comparable performances in terms of their accuracy.

Utility

The overall benefit of NAATs is that they amplify a small amount of viral target RNA to a detectable level. They are more sensitive than an antigen-based test and much faster and safer than performing viral culture. However, a significant drawback is that they can detect viral RNA shedding for an extended period in some patients, even after they are no longer symptomatic and presumed no longer infectious.

SARS-COV-2 TESTING – SEROLOGY TESTING

Overview

Serological tests detect antibodies present in the blood and thus can reveal any current or previous infection. Antibody tests must be specific enough to prevent cross-reaction with antibodies against other pathogens. For SARS-CoV-2, antibodies against S and N proteins are commonly tested, where the antibodies against two subunits S1 and S2 of the S protein can be tested individually or together. The antibody isotypes in SARS-CoV-2 tests are IgM, IgG, and IgA, although IgM and IgG antibodies are generally tested individually or together as total antibodies.

Antibody responses generally occur between 10 to 21 days after infection, with mild cases potentially taking upwards of four weeks. In a recently published study, COVID-19 specific IgM and IgG antibodies were first detectible 3–4 and 5-6 days post-symptom onset, respectively, with a marked increase in antibody detectability and test sensitivity 14 days post-symptom onset.[10] Therefore, such tests are not useful for early screening or initial patient visits.

It is unknown how long COVID-19 specific antibodies remain detectable and whether they correlate to any long-term protection. A recently published study suggests that most patients showed sharp declines of COVID-19 specific IgG antibodies within two to three months after infection onset.[11] A possible new area of inquiry is the study of cellular immunity. A study on medRxiv done by Staines et al. has found that a small percentage of infected patients do not develop COVID-19 antibodies at all, suggesting that the immune response in these patients could be through separate antigens or mediated through T cells.[12]

Testing Platforms

Of the few dozen serology tests currently in the market, four particular testing platforms are currently being used to analyze SARS-CoV-2: the lateral flow assay (LFA), the enzyme-linked immunosorbent assay (ELISA), the chemiluminescent assay (CLIA), and the cyclic enhanced fluorescence assay (CEFA).

LFAs prioritize speed and ease of use, offering a flexible and cost-effective method of obtaining a result. Nevertheless, limitations of LFAs include the difficulty to perform large-volume testing and multiple analyte testing. ELISA tests provide standard antibody titers; however, the tests are rather labor-intensive, if not assisted by automation. As opposed to other immunoassays, CLIAs measure photons of light to discern a result, leading to its high sensitivity and specificity. While these tests require expensive instruments and highly purified reagents, the high sensitivity permits the use of very small reagent volumes per test, keeping the

assay cost-effective.[13] The main advantage of CEFA tests lies in the cyclic amplification of the fluorescence signals to detect antibodies sensitively and specifically, and have shown promising clinical utility in evaluating the immune response in infected and convalescent patients.[14]

While current serology testing serves as an excellent indicator of prior or current infection, they do not directly assess the neutralizing capabilities of the antibodies. For this purpose, neutralizing antibody assays aim to identify antibodies that recognize the SARS-CoV-2 virus and block its host cell entry.

There are two recognized types of neutralizing antibody tests: virus neutralization tests (VNT) and pseudovirus neutralization test (pVNT). VNTs utilize SARS-CoV-2 viruses from clinical isolates and can only be performed in a Biosafety Level 3 laboratory by highly trained personnel. Alternatively, pVNTs use recombinant pseudoviruses that express the S protein of SAS-CoV-2 to construct the spikes on the viral surface.[15] A specific example is the pseudovirus luciferase assay (PVLA), where the inhibition of viral entry into cells by the neutralizing antibody correlates to the decreased luciferase signals in the cells. pVNTs are safer, simpler, and more accurate than conventional assays.[16]

Utility

Serologic testing is primarily used to detect the presence of antibodies specific to a given virus and is therefore not a good indicator of current infection, as a positive result indicates that a patient is either in the late phase of the disease or he/she may have been infected in the past. Nevertheless, using a serological test alongside a NAAT has proven effective in providing more accurate diagnoses.[17]

Serologic testing is frequently used for disease surveillance and is thus an integral part of policymaking, both on the governmental and communal level. It is also utilized in transfusion medicine (e.g. with the convalescent plasma treatment) to determine the antibody titer in the unit. Finally, serologic testing will be useful in verifying whether or not a vaccine incites the desired immune response. Distinguishing the immune response to the vaccine from that to the real infection will be challenging in individuals inoculated by inactivated virus-based vaccines, but the presence of RBD or S-protein antibodies and absence of N-protein antibodies should be sufficient to identify an immune response to the S-protein based vaccines.

Other Assays

Currently, NAAT and serologic tests are the most prevalent assays used to diagnose or screen COVID-19. But due to the continued shortage of available tests, there has been a continued push to utilize existing and novel methods for viral detection.

Antigen-based tests are diagnostic tests designed to detect fragments of viral proteins. They utilize similar technology to some serology tests, such as the LFA and the ELISA. The advantage of antigen tests is that they can be performed near the patient without the need for a high-complexity laboratory, and a large number of tests can be manufactured and widely distributed due to their simpler design.[18] However, they do suffer from a lack of sensitivity and specificity compared to NAATs. For the first time, the CRISPR-based technology has been authorized under the FDA EUA for direct patient use. The assay uses the SHERLOCK (Specific High-sensitivity Enzymatic Reporter unLOCKing) method to program a CRISPR molecule to specifically detect the presence of a specific SARS-CoV-2 genetic signature.[19] The advantage of this technology is that it is faster than RT-PCR and can potentially be scaled up to test a large volume of samples. Finally, there are increasing in the development of simple, daily COVID-19 tests. One such test is the paper-strip test, in which a sample of spit in a saline solution would be tested with a strip of paper embedded with protein.[20] Such tests have shown promise and can potentially circumvent some of the issues surrounding the current testing strategies such as cost and testing availability.

CLOSING REMARKS

As it stands, personal hygiene and social distancing procedures are the most effective preventative measures against SARS-CoV-2. When it comes to testing, NAAT and serology testing are the mainstays in clinics and hospitals. In the competitive market of COVID-19 testing, more and more assays are becoming available and being authorized by the regulatory agencies. All the current and emerging assays will keep being used under specific medical and epidemiologic circumstances until the global population reaches herd immunity either by the virus or by the vaccine. The swift response of the medical diagnostic industry to the pandemic highlights the importance of basic biomedical research which is constantly providing scientific and technological knowledge for the health care industry to develop advanced tools and agents to fight diseases and safeguard our population.

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Authors

Eric W. Tang, Department of Pathology and Laboratory Medicine, Alpert Medical School of Brown University, Providence, RI.

April M. Bobenchik, PhD, Department of Pathology and Laboratory Medicine, Alpert Medical School of Brown University, Providence, RI.

Shaolei Lu, MD, PhD, Department of Pathology and Laboratory Medicine, Alpert Medical School of Brown University, Providence, RI.

Correspondence

Shaolei Lu, MD, PhD
Director, Clinical Immunology Laboratory
Lifespan Academic Medical Center
Pathology and Laboratory Medicine
Alpert Medical School of Brown University
Providence, RI 02903
slu@lifespan.org

April M. Bobenchik, PhD, D(ABMM)
Associate Director, Clinical Microbiology
Lifespan Academic Medical Center
Pathology and Laboratory Medicine
Albert Medical School of Brown University
Providence, RI 02903
april_bobenchik@brown.edu

COVID-19 and Kidney Injury

MATTHEW R. LYNCH, MD; JIE TANG, MD, MPH, MSc

ABSTRACT

BACKGROUND: Acute kidney injury (AKI) has been reported as a complication of COVID-19. However, the epidemiology, management, and associated outcomes have varied greatly between studies. The pathophysiology remains unclear.

SUMMARY: The etiology of AKI in the setting of COVID-19 appears multifactorial. Systemic effects of sepsis, inflammation, and vascular injury likely play some role. Furthermore, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptor, highly expressed in the kidney, providing a route for direct infection. Older age, baseline comorbidities, and respiratory failure are strong risk factors for the development of AKI. Regardless of etiology, AKI carries a significantly increased risk for in-hospital mortality, especially in those with critical illness. Currently, management of AKI in patients with COVID-19 remains supportive.

KEY MESSAGES: AKI is common in patients with COVID-19. Future studies are needed to examine the response to anti-viral treatment as well as long-term renal outcomes in patients with AKI.

KEYWORDS: acute kidney injury, COVID-19, ACE2

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) outbreak, first reported on December 8, 2019 in Wuhan, China, was designated as a pandemic by the World Health Organization (WHO) on March 11, 2020. This disease, recognized as an infection by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread quickly throughout the world. As of August 4, 2020, close to 18 million laboratory-confirmed cases had been documented globally, with nearly 700,000 deaths worldwide.[1] The mortality rates vary significantly among studies from 0.3% to 10%, partially reflecting the differences in local policy, access to diagnostic testing, and health care resources and response. Clinical presentations of COVID-19 can range from asymptomatic infection, self-limited influenza-like symptoms, acute pneumonia to severe respiratory failure.

The ongoing COVID-19 pandemic carries serious medical, psychosocial, and economic consequences. Understanding its pathophysiology, clinical course, management strategy and therapeutic response are of paramount importance. Here, we will synthesize the current literature on the acute kidney injury (AKI) in COVID-19, and discuss its epidemiology, pathogenesis, clinical features, outcomes, and management strategies.

ACUTE KIDNEY INJURY

COVID-19 has life-threatening effects far beyond its respiratory manifestations. An initial single center cohort of 116 confirmed COVID-19 cases from China with a median age 54, 11 of whom had severe infection, failed to show incident AKI. [2] However, subsequent studies have reported a cumulative incidence of AKI in COVID-19 ranging from 0.9% to 29%, with patients who were critically ill more likely to develop AKI. A summary of some of these studies can be seen in **Table 1**.

The earliest publication identifying AKI as a consequence of COVID-19 came from China, involving a large cohort of 1099 hospitalized patients with confirmed COVID-19 and a median age of 47. Five percent of this cohort was critically ill requiring ICU admission. Interestingly, these patients were relatively healthy at baseline: 7% had history of diabetes mellitus (DM), 15% hypertension, and only 1% chronic kidney disease (CKD). AKI was rare with an incidence rate of 0.5%.[3] In a second Chinese cohort from Wuhan, Cheng et al examined 701 hospitalized patients with COVID-19, of which 10% required intensive care.[4] These patients were older and with more baseline comorbidity; AKI was found in 5.1% of patients. Baseline CKD was a strong risk factor for the development of AKI. Consistent with this, Wang et al reported a 4% AKI incidence rate in another, smaller Chinese cohort with similar age and baseline comorbidity.[5]

In the United States, two large cohorts from metropolitan New York have helped define the epidemiology of AKI here. A cohort of 5,449 patients from 13 academic and community hospitals, with heavier burden of comorbidities than in the Chinese cohorts, had an incident AKI rate of 36.6%.[6] AKI developed early in the course, with more than one third of those with AKI either arriving with it or developing it within 24 hours of admission. AKI was primarily

Table 1. Summary of published studies on AKI in patients with COVID-19

Studies	Origin	N	Age	DM	HTN	CKD	ICU	AKI	Mortality (overall)
Cheng et al[4]	China	701	63 (50–71)	100 (14%)	233 (33%)	14 (2%)	73 (10%)	36 (5%)	113 (16%)
Wang et al[5]	China	138	56 (42–68)	14 (10%)	43 (31%)	4 (3%)	36 (26%)	5 (4%)	6 (4%)
Guan et al[3]	China	1099	47 (35–58)	81 (7%)	165 (15%)	8 (1%)	55 (5%)	6 (0.5%)	15 (1%)
Hirsch et al[6]	USA	5449	64 (52–75)	1797 (33%)	3037 (56%)	N/A	1395 (26%)	1993 (37%)	888 (16%)
Yang et al[22]	China	52	60 (13)	9 (17%)	N/A	N/A	52 (100%)	15 (29%)	32 (62%)
Chan et al[7]	USA	3235	N/A	N/A	N/A	N/A	815	1406 (46%)	N/A

Data was reported as median (IQR), mean (SD) or number (%)

seen in COVID-19 patients with respiratory failure (23.2% in ventilated patients vs. 0.2% in non-ventilated patients). Of patients who required ventilation and developed AKI, 52.2% had the onset of AKI within 24 hours of intubation. Among patients with AKI, 14.3% received renal replacement therapy (RRT), and the vast majority (96.8%) were on ventilators. Risk factors for AKI included older age, DM, cardiovascular disease, black race, hypertension, and need for ventilation and vasopressor support. For patients who developed AKI and survived to hospital discharge, the median peak serum creatinine was 2.34 mg/dL with a median of 1.70 mg/dL at discharge. In another large cohort of 3,235 hospitalized COVID-19 patients from New York, AKI occurred in 46% patients with 20% requiring RRT.[7] The cumulative incidence of AKI (admission plus new cases) in patients admitted to the intensive care unit was 68%. In the entire cohort with AKI, the proportion with stages 1, 2, and 3 AKI were 35%, 20%, 45%, respectively. In those needing intensive care, the respective proportions were 20%, 17%, 63%, suggesting an association between severe AKI and severe illness. Of those with AKI in the ICU, 34% received renal replacement therapy. Independent predictors of severe AKI in this cohort included CKD, higher systolic blood pressure, and potassium at baseline.

In a meta-analysis of nine studies (eight from China, one from United States) of hospitalized patients with COVID-19, two of the studies included only patients admitted to the intensive care unit.[8] In an overall hospital setting, the incidence rates of AKI varied from 0% to 14.7%, with a pooled incidence rate of 7%. In the six studies that reported RRT use, 0.5%–7.3% of patients required RRT, with a pooled RRT incidence rate of 2%. Four studies reported the incidence of AKI in the ICU setting, with rates ranging from 8.3% to 28.8% and a pooled incidence rate of 19%. Only three studies reported RRT use in an ICU setting, with rates of RRT use ranging from 5.6% to 23.1% with a pooled rate of 13%. These studies reiterate that the risk of AKI and need for RRT were much higher in COVID-19 patients who were critically ill.

In addition to AKI from acute tubular necrosis, the possibility of glomerular disease from COVID-19 has been suggested with the presence of hematuria and proteinuria (**Table 2**). In the Chinese cohort by Cheng, et al, 44% of patients had proteinuria and 27% had hematuria at presentation.[4] In the US cohort by Hirsch et al, 42% had proteinuria and 46% had hematuria.[6]

Table 2. Summary of COVID-19 related kidney pathological findings in patients with acute kidney injury. Summarized from 9–11.

Tubulointersitial
Acute Tubular Injury
Vascular
Cortical infarction
Microthrombi
Glomerular
Anti-Glomerular Basement Membrane Nephritis
Collapsing Focal and Segmental Glomerulosclerosis
Membranous Nephropathy
Minimal Change Disease

PATHOLOGICAL FINDINGS

According to an autopsy series from Wuhan, China, light microscopy of the kidney tissue from those with AKI (nine patients total) showed findings consistent with acute tubular injury, the pathologic correlate of acute tubular necrosis (ATN): loss of brush border, vacuolar degeneration, luminal dilatation, and in some cases, areas of necrosis and detachment of tubular epithelium.[9] Pigmented tubular casts, possibly due to rhabdomyolysis, were also seen. Distal tubules and collecting ducts showed only occasional cellular swelling and edematous expansion of the interstitial space without significant inflammation. Acute pyelonephritis was observed in some patients. Diffuse erythrocyte aggregation and obstruction were present in peritubular and glomerular capillaries without distinct fragmentation of erythrocytes, or features of fibrin thrombi. In glomeruli, segmental fibrin thrombus in capillary loops were found with severe endothelial swelling and injury, along with other ischemic changes and pseudocrescent appearance. Immunofluorescence showed nonspecific IgM and C3 trapping. Under electron microscopy, paramesangial and subendothelial electron dense deposits with segmental mesangial interposition and increased lamina rara interna were present in one case, and

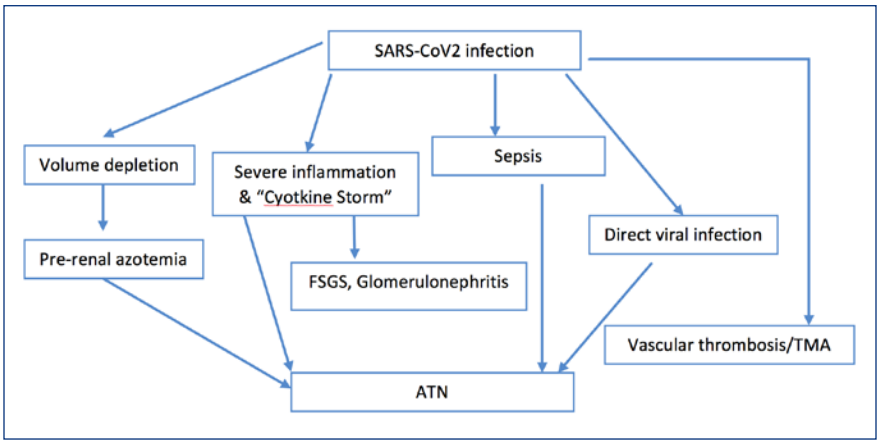
scattered subepithelial deposits were noted in another case. Both patients did not have evidence of bacterial infections, suggesting a direct association with SARS-CoV-2 infection. No other diagnostic electron-dense deposits were detected.

Two separate biopsy series taken from patients in the United States who developed AKI in the setting of COVID infection has found new-onset immune-mediated glomerular disease[10] and the presence of collapsing focal and segmental glomerulosclerosis in patients with two apolipoprotein L1 risk variant genes.[11] No intracellular viral particles were observed in these cases.

PATHOGENESIS

The causes of AKI are likely multifactorial (**Figure 1**). In addition to common processes related to systemic infection including poor renal perfusion from volume depletion or blood flow shunting, direct cytopathic viral infection, severe inflammation and cytokine storm resulting from SARS-CoV2 infection have all been implicated.[9,12,13] The contribution of each of these entities to tubular injury remains under investigation. As noted above, the vast majority of cases are caused by ATN, although some glomerular pathologies have been found. In the cases of glomerular involvement, the absence of viral particles in these series suggests cytokine-mediated kidney damage as the likely etiology, but further investigation to confirm this is required. Lastly, COVID-19 has been shown to cause endothelial injury and is associated with hypercoagulable state,[14] thus renal thrombotic microangiopathy (TMA) or microvascular thrombosis can also contribute to the development of AKI.

Figure 1. Pathogenesis of AKI in COVID-19



DIRECT VIRAL INFECTION OF KIDNEY

Similar to SARS-CoV, the spike (S) protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), its host cell target for direct invasion. The viral entry into the host cells also require viral S protein priming by cellular proteases, the TMPRSS family, which entails S protein cleavage and allows fusion of viral and cellular membranes.[15] ACE2 is highly expressed in the kidney, similar to the epithelial cells of lung and gastrointestinal (GI) tract, indicating kidney as a potential target organ.[16] Via single-cell transcriptome analysis, Pan et al demonstrated that both ACE2 and TMPRSS genes were significantly co-expressed in podocytes and renal proximal tubules, and the levels of expression were higher than that of lung tissue and GI tract.[16]

The more direct evidence of viral kidney infection came from an autopsy series in Wuhan, China. Su et al reported pathologic findings in the kidneys from 26 patients died of SARS-CoV-2 infection.[9] Nine of the 26 had clinical evidence of kidney involvement with increased serum creatinine and/or new-onset proteinuria. Electron microscopic examination revealed clusters of coronavirus particles with distinctive spikes in the tubular epithelial cells and podocytes. The immunostaining for SARS-CoV-2 nucleoprotein was positive in renal tubules, as well. There was also strong focal viral staining in parietal epithelial cells as well as occasional weaker staining in podocytes. As expected, the expression of ACE2, the receptor of SARS-CoV-2, was found to be upregulated in these patients infected with COVID-19. Compared with non-COVID-19 infected control, ACE2 expression was prominent in proximal tubular cells, particularly in areas with severe tubular injury. [9]

CYTOKINE STORM AND INFLAMMATION

Induction of an inflammatory response is a known trigger for AKI, and it is initiated through both pathogenic and non-pathogenic processes. During inflammation, pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) bind to Pattern Recognition Receptors (PRRs) expressed in cells of multiple organs, including renal tubular epithelial cells, and induce cell damage.[17] As a matter of fact, there is a strong association between cytokine levels (interleukin (IL)-6, IL-10, and macrophage migration inhibitory factor) and the development of sepsis-induced AKI.[18]

An inflammatory cytokine profile resembling hemophagocytic lymphohistiocytosis has been found in severe cases of COVID-19, characterized by increased IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α.[12] According to a retrospective study of 150 COVID-19 cases in Wuhan, China, elevated levels of inflammatory markers such as ferritin, C-reactive protein and IL-6 were present in severe COVID-19 cases and predicted fatality,[13] suggesting

an important and detrimental role of virally driven hyperinflammation and cytokine storm in SARS-CoV-2 infection. The higher risk and severity of AKI seen in severe SARS-CoV-2 infections supports the role of inflammation in the pathogenesis of AKI.

VASCULAR INSULT AND COAGULATION DISORDER

Cardiovascular complications are rapidly emerging as a key threat in COVID-19. Direct endothelial cell infection and endothelitis have been demonstrated in SARS-CoV2 infected patients.[19] Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction. Injured endothelial cells produce a decreased quantity of vasodilators, such as nitric oxide, resulting in a more pronounced response to vasoconstrictors. This leads to a redistribution of blood flow.[17] The imbalance between vasoconstrictors, vasodilators and oxidative stress at the endothelial level is believed to be a major contributor to the development of AKI.

The development of coagulopathy in the forms of deep venous thrombosis and pulmonary embolism are well-recognized features of COVID-19, and is one of the most significant poor prognostic factors.[20] Therefore, augmented vasoconstriction, small vessel occlusion due to activated endothelial cells and activation of the coagulation system can result in renal TMA and compromised microvascular perfusion. Lastly, patients with severe COVID-19 who experienced abnormal clotting have been shown to carry positive antiphospholipid antibodies, suggesting secondary antiphospholipid syndrome might also account for COVID-19-associated thrombotic events.[14]

MANAGEMENT OF AKI IN THE SETTING OF COVID-19

To date, there are limited data to guide the clinical treatment strategies for COVID-19 and its renal complications. For COVID-19, the general approaches include controlling the source of infection, use of personal protective equipment to reduce the risk of transmission, early diagnosis/isolation, and symptomatic supportive care for affected patients. Antibacterial agents are ineffective, and no antiviral agents have been clearly proven to be beneficial for treating COVID-19.

In those with AKI, early detection and adoption of kidney protective measures are important to reduce mortality and improve prognosis. Strategies have been applied including hemodynamic support, avoidance of nephrotoxic drugs, aggressive management of electrolyte and acid-base derangements, and renal replacement therapy whenever it is indicated.

For patients who require dialysis, clinicians can decide to provide either intermittent hemodialysis, continuous renal replacement therapy (CRRT) or acute peritoneal dialysis based on a patient's clinical status and the facility's resources. Increased thrombosis of catheters or extracorporeal filters during CRRT has been recognized and specific anticoagulation protocols have been developed to mitigate the hypercoagulable state.[21]

PROGNOSIS OF COVID-19 PATIENTS WITH AKI

AKI has a major impact on survival among hospitalized COVID-19 patients (**Table 1**). In a large cohort from New York, in-hospital mortality among patients with AKI was 41%, the rate increased to 52% in those admitted into intensive care with AKI.[7] The adjusted odds ratio for mortality associated with AKI was 9 overall and 20.9 in patients receiving intensive care.

In another cohort from New York, among 1,993 patients who developed AKI during the hospitalization, 26% of patients were discharged and 35% died.[6] Of those with AKI, risk of death and prolonged hospital stay was related to severity of AKI: 57% with stage 1 AKI died or were still hospitalized during the study period as compared with 80% with stage 2 and 94% with stage 3. Among the 285 patients who required RRT, 157 died and only 9 were discharged from the hospital. Another 119 were still undergoing treatment in the hospital, with 108 still on RRT (90.8%).

Outside United States, Cheng et al examined 701 hospitalized COVID-19 patients in Wuhan, China, and found AKI carried a significantly increased risk for in-hospital mortality.[4] Cox proportional hazard regression confirmed that baseline CKD, AKI, proteinuria and hematuria were all independent risk factors for in-hospital death after adjusting for age, sex, disease severity, comorbidity and leukocyte count. Therefore, both baseline CKD and AKI during hospitalization in patients with COVID-19 is clearly associated with higher in-hospital mortality.

CONCLUSION AND FUTURE PERSPECTIVES

The COVID-19 pandemic is far from over with millions of cases reported worldwide, and over 200,000 new cases reported daily.[1] The pathogenesis of AKI has not been clearly established in this patient population. The therapeutic responses of patients with AKI to various medications under clinical investigation are unclear. The impact of AKI on disease duration, viral clearance, risk of CKD and long-term survival are also uncertain. As the healthcare system and resources become overwhelmed by COVID-19 pandemic, the access to routine CKD care and kidney transplantation can be negatively affected and its short-term and long-term impact warrants further investigation. Lastly, an evidence-based comprehensive management guideline is desperately needed to win this battle.

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Authors

Matthew R. Lynch, MD, Division of Kidney Diseases and Hypertension, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

Jie Tang, MD, MPH, MSc, Division of Kidney Diseases and Hypertension, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

Correspondence

Jie Tang, MD, MPH, MSc
Rhode Island Hospital
APC 920, 593 Eddy Street
Providence, RI 02903
401-444-6844
jie_tang@brown.edu

COVID-19 and ESKD, A Rapid Review

ANKUR D. SHAH, MD; NATHAN CALABRO-KAILUKAITIS, MD

ABSTRACT

In 2020, the COVID-19 pandemic has ravaged the world. Individuals with end-stage kidney disease (ESKD) are at higher risk due to impaired immunity, comorbid conditions, and dependence on travel to medical care settings. We review the salient features of COVID-19 in this population, including the risk of infection, disease course, changes in dialysis unit management, use of investigatory medications, access considerations, home dialysis, and capacity planning.

KEYWORDS: coronavirus, COVID-19, end-stage kidney disease, dialysis

INTRODUCTION

The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has devastated the United States and the world in 2020. Patients with end-stage kidney disease (ESKD) are at particular risk, owing to both dysfunction of innate and adaptive immunity and a significant burden of comorbid conditions.[1] Management of this vulnerable population is complex, and in this paper, we review key aspects including risk of infection, risk of mortality, changes in operations including medications and access, and contingency planning.

RISK OF INFECTION

The Centers for Disease Control (CDC) guidance states that while everyone is at risk of COVID-19, certain populations have increased risk for severe illness, including older adults, individuals with chronic kidney disease, individuals with chronic obstructive pulmonary disease, solid organ transplant recipients, those with obesity, cardiac conditions, sickle cell disease, and type 2 diabetes mellitus. Patients on dialysis have weakened immune systems and high rates of cardiac conditions and type 2 diabetes mellitus in addition to their own kidney dysfunction.[2]

A preliminary Medicare COVID-19 snapshot of claims and encounter data from services rendered through May 16, 2020 with claims received by June 11, 2020 found the highest burden of COVID-19 in patients with ESKD. 2,614 cases were found per 100,000 beneficiaries compared to the general population rate of 518 cases per 100,000. Burden increased further to 3,953 per 100,000 in those with dual Medicare and Medicaid eligibility. 51.3% required hospitalization.[3] Individual centers have published their experience as well, with significant heterogeneity.[3] Dialysis Clinic, Inc. (DCI), a non-profit dialysis organization caring for approximately 15,000 patients in outpatient dialysis units, noted as of July 5, 2020, 566 (3.7%,) patients in outpatient clinics had tested positive for COVID.[4] 39.2% of cases were from group homes. The majority of new cases were reported in April, 2020; however, there was a recent increase in the trend of incident cases.[4]

CLINICAL FEATURES AND MORTALITY

Early in the pandemic it was theorized that the clinical course could either be more exaggerated than the general population due to high rates of comorbid conditions and the basal mortality of the ESKD population or that the immunocompromised state may attenuate the inflammatory response of COVID-19 and thus provide a milder syndrome. The literature is currently rapidly evolving to better delineate the course.

Three hospitals in New York, Columbia University Irving Medical Center, Moses Hospital, and Weiler Hospital, have reported outcomes of patients admitted with end stage kidney disease. Pooled mortality was 28.9% in a total of 173 hospitalized patients, the majority of whom dialyzed via in center hemodialysis. Symptoms of cough, fever, and dyspnea were present in less than fifty percent of patients. Risk factors for mortality reported by the groups included greater age, higher comorbidity index, degree of lymphopenia, C-reactive protein elevation, LDH elevation, IL-6 elevation, and ferritin elevation. Mortality was 86.7% in those requiring intensive care unit level of care.[5,6]

While these single center reports provide granular detail, they are limited by the nature of the pandemic as different areas of the US have had different experiences. The DCI COVID-19 cohort, a national cohort, reported 21.3% mortality.[4] Amongst those living in group homes, mortality was higher at 25.7%.[4] Notably the population from which this cohort is derived is outpatient dialysis units, while the population of the above cohort was hospitalized dialysis patients, which accounts for the variability in mortality.

The international experience has been described as well in an early report from Wuhan, China demonstrating the tenuous state of dialysis patients with COVID-19. During a 2-month study period, 42 of 230 hemodialysis patients were diagnosed with COVID-19, 10 of the 42 died during the epidemic. Only 2 deaths were associated with respiratory failure, with the main causes of death being cardiovascular events and hyperkalemia, highlighting to the nephrology community the risk of underdialysis in reaction to COVID-19.[7] This was followed by a more comprehensive analysis from Wuhan, China in which 154 of 7154 maintenance hemodialysis patients were reported to test positive for COVID-19 from January to March 10, 2020. Of the 154 patients diagnosed with COVID-19, 23 did not consent to analysis of their data. Fever, cough, and dyspnea were only present in 51.9%, 37.4%, and 26% of patients respectively. 82.1% presented with ground glass opacities on computerized tomography of the chest. 13.8% progressed to develop acute respiratory distress syndrome. Mortality was 31.2% amongst 131 patients.[8]

Four Italian centers in the Brescia Renal COVID Task Force have also shared their experience, reporting the outcomes of 643 hemodialysis patients. 94 (15%) patients were positive for COVID-19. 39% required hospitalization. Treatments attempted included antivirals, hydroxychloroquine, glucocorticoids, and tocilizumab. Mortality was 25.5% in the cohort.[9] History of fever, cough and a C-reactive protein higher than 50 mg/l at presentation were associated with the risk of death.[9]

CHANGES IN DAY-TO-DAY OPERATIONS

The need to care for COVID-19 patients who do not require hospitalization has presented a challenge for dialysis units. Dialysis units are congregate settings in which in-person encounters are necessary. Considerations that must be taken into account during the COVID-19 pandemic include the safety of this vulnerable group of patients as well the need to maintain a healthy staff of highly trained personnel including technicians, nurses, and physicians to provide continued dialysis care. In addition to the Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings, the CDC has released guidance for outpatient hemodialysis units.

Broadly, the CDC recommendations have addressed topics

Table 1. CDC Guidance for Infection Prevention and Control for Patients with Suspected or Confirmed COVID-19 in Outpatient Hemodialysis Facilities[10, 11]

Key Area	Recommendations
Universal Face Covering	Mask for health care personnel, cloth face covering or mask for patients
Early Recognition and Isolation of Individuals with suspected or known COVID-19	Non-punitive sick leave policies Awareness of the possibility of asymptomatic transmission (highlighting importance of universal face mask policy and application of prevention practices to all patients (hand hygiene, surface decontamination, and distancing) Identification of patients with fever or symptoms of COVID-19 before entrance into treatment area Patients should call ahead if they have fever or symptoms of COVID-19 Facility should provide instruction regarding maintaining a distance of at least 6 feet from all other persons, hand hygiene, use of face covering, cough etiquette. Facility should post signs at clinic entrances with instruction for patient with fever or symptoms of COVID-19 to alert staff Facilities should position supplies (tissues, no-touch receptacles, and hand hygiene supplies close to dialysis chairs and nursing
Placement of Patients	Facilities should have space in waiting areas for patients to sit separated by at least 6 feet from other patients. Bring patients with known or suspected COVID-19 to treatment area as soon as possible to minimize time in the waiting area. Dialyze patients with known or suspected COVID-19 in a separate room. If not possible, patients with known or suspected COVID-19 should be dialyzed in an end-of-row or corner station. Patients with known or suspected COVID-19 should be separated by at least 6 feet from the nearest patient station. If more than one patient is suspected of having or confirmed to have COVID-19 consideration should be given to cohorting these patients and HCP providing care for them to a section of the unit and/or to the same shift
Personal Protective Equipment	HCP caring for patients with suspected or confirmed COVID-19 should use an N-95 or higher level respirator if available. If a shortage exists, respirators should be reserved for situations when respiratory protection is most important (i.e. performance of aerosol generating procedure). Gloves Eye protection Isolation gown
Disinfecting	Current procedures for routine disinfection and cleaning of dialysis stations are acceptable for patients with COVID-19 (though important to validate activity of surface disinfectant is active against SARS CoV-2). Staff should be trained and have competency assessed for cleaning and disinfection procedures.

including masking, early recognition of individuals with suspected or confirmed COVID-19, placement of patients, personal protective equipment (PPE), and disinfecting. A summary of the CDC guidance can be found in **Table 1.**

Similarly, The American Society of Nephrology (ASN) has also provided information for screening for and management of COVID-19 in the outpatient dialysis facility closely based on the CDC guidance.

The experiences of several international dialysis centers have been described. In Lombardy, Italy, 18 hemodialysis patients were infected then isolated immediately and treated in a dialysis ward, separate from the main dialysis ward. None of the health care staff had been infected at the time of reporting, nor had any of the other, approximately 200 total hemodialysis patients developed known infection. In a second center, four of 170 patients were infected and after isolation no other case had been diagnosed in staff or another patient. Testing was done in symptomatic cases and following the first positive case, all patients were required to wear surgical masks.[12]

A second later report from a hemodialysis center in Lombardy Italy suggested that preventive measures were helpful in preventing the spread of SARS-CoV-2. 33 of 188 HD patients in the outpatient centers had positive nasopharyngeal swab for SARS-CoV-2. Prior to results, SARS-CoV-2 positive patients received HD treatments in rooms with patients who had had a negative swab. After receiving swab results, cohorting of patients was implemented. The results were no additional symptomatic infections in patients who had previously had negative swabs and none in the health care staff.[13]

A multi-center study conducted in Korea investigated HD with cohort isolation for close contacts of patients with COVID-19 on the prevention of secondary transmission of the SARS-CoV-2 in HD units. 11 patients on HD and seven health care workers from 11 HD centers were diagnosed with COVID-19. 302 close contacts based on the epidemiologic investigation were enrolled and cohort isolation HD was performed among all close contacts in seven centers for a median of 14 days. During cohort isolation, only two health care workers and no patients were diagnosed with SARS-CoV-2.[14]

In terms of de-isolation, fourteen days may not be an appropriate threshold. Dudreuilh et al reported the deisolation experience of a single center in the NHS trust in London. 14 of 34 patients (41%) of COVID-19 positive patients did not clear the virus by day 15. Five patients cleared the virus later (median of 18 days), and 9 patients had had only one negative swab at the end of follow-up or had remained positive.[15] Notably prolonged viral shedding may not represent an infectious individual as it is unclear if individuals with prolonged shedding are shedding inactive viral particles or functional virions.

EXPERIMENTAL MEDICATION CONSIDERATIONS

Several medications have been and are being studied as anti-viral and anti-inflammatory agents in the management of COVID-19. Agents such as remdesivir, hydroxychloroquine, glucocorticoids, and tocilizumab have all been the focus of recent or active randomized controlled trials.

Remdesivir, a prodrug initially developed for treatment of ebolavirus that inhibits viral replication, has been studied in the management of COVID-19 based on in-vitro and in-vivo animal studies showing activity against coronaviridae. The FDA emergency use authorization recommends consideration of potential risks and benefits in individuals with estimated glomerular filtration rate less than 30 milliliters per minute. Intravenous remdesivir is delivered with an excipient, sulfobutylether-β-cyclodextrin (SBECD), due to its water insolubility. Animal studies have shown that SBECD accumulation when delivered in doses 50-100 times the dose from a 5-10 day course of remdesivir can be nephrotoxic. SBECT is also the excipient of intravenous voriconazole, a setting in which short term use has been found to be safe. SBECD is cleared by hemodialysis as well. Consideration of risk-benefit should be given prior to withholding remdesivir in patients with ESKD.[16,17]

Hydroxychloroquine, an antimalarial commonly used for its anti-inflammatory properties, has been the subject of great debate in COVID-19. It is highly protein bound, with hepatic metabolism and renal clearance accounts for only fifteen to twenty five percent of excretion. Dialytic clearance is minimal and supplemental dosing is not necessary.[17]

Dexamethasone, a long acting glucocorticoid with potent anti-inflammatory properties, was found to reduce mortality in the Randomized Evaluation of Covid-19 Therapy trial.[18] Dexamethasone is hepatically metabolized with minimal urinary excretion. Safety has been demonstrated in individuals receiving renal replacement therapy and dose adjustments or supplementary doses are not required in dialysis patients.[17]

Tocilizumab, an antagonist of the interleukin-6 receptor leads to a reduction in cytokine production and is used frequently in cytokine release syndrome from T-Cell therapy. Efficacy and safety have not been demonstrated in individuals with moderate to severe kidney impairment. It is not believed that clearance is influenced by kidney function and dose adjustments are not typically needed.[17]

VASCULAR ACCESS CONSIDERATIONS

Establishing vascular access in preparation for chronic hemodialysis remains essential during the COVID-19 pandemic. Early in the pandemic, CMS released guidance recommending delay of any non-essential surgeries. The American Society of Diagnostic and Interventional Nephrology and the Vascular Access Society of the Americas have issued a joint statement exclaiming dialysis accesses are the "lifeline" for

patients with ESKD and suggested that lack of access would lead to complications and demise.[19]

In response to feedback regarding difficulty scheduling placement or repair of arteriovenous fistulas, arteriovenous grafts, and intravascular catheters, CMS clarified their stance and deemed establishment of vascular access essential to receiving hemodialysis noting the risk of morbidity, mortality, and infection that would be expected with temporary hemodialysis catheters.

FUTURE CONTINGENCY PLANS AND HOME DIALYSIS

The data presented previously highlights the opportunity to lower the risk of COVID-19 infection amongst the vulnerable ESRD patient population. Home dialysis therapies including peritoneal dialysis (PD) and home hemodialysis (HHD) offer the potential advantage of minimizing inter-personal contact and transmission of COVID-19 as compared to in-center hemodialysis (HD). However, in 2017, home therapies constituted less than 10% of treatment for ESRD. 62.7% of all prevalent ESRD patients in 2017 were receiving HD therapy. Only 2.0% of these patients used HHD. 7.1% of ESRD patients in the same year were being treated with PD.[2]

Snapshot data on infection rates in the Veneto region and Vicenza referral area of Italy in April, 2020 showed a lower percentage of COVID-19 positive peritoneal dialysis (PD) patients compared to hemodialysis patients. Aggregate data showed four of 627 (0.64%) of PD patients were positive for COVID-19 while 36 of the 1,991 hemodialysis patients (1.81%) were positive for COVID-19. Noteworthy was that one of the COVID-19 positive PD patients was thought to have acquired the infection from a daughter who worked in a nursing home.[20]

The COVID-19 pandemic has prompted the use of telehealth in the management of home dialysis patients Telehealth offers the obvious advantage of limiting physical congregation as compared to traditional medical visits. In March 2020, CMS released a toolkit for ESKD providers to help with the establishment and operation of telehealth programs.

Telehealth has been successfully used during the COVID-19 pandemic as a substitute for in-person monthly clinic visits for home dialysis patients. The Rogosin Institute is an independent dialysis provider affiliated with New York Presbyterian Hospital and had a home dialysis population of 210 patients (150 on PD and 60 on HHD). All patients were offered telehealth visits for their monthly visit from March 1, 2020. 78 telehealth monthly visits were performed. Anecdotally the institute's home dialysis patients were satisfied with telehealth as a tool to potentially reduce COVID-19 exposure though no formal survey was conducted, nor any clinical outcome data reported.[21]

While the evidence is clearly limited thus far, a commentary in the Journal of the international Society for Peritoneal Dialysis recommended consideration of PD as a preferred option for individuals with advanced kidney disease.[22]

CONCLUSION

ESKD and COVID-19 are both conditions with significant morbidity and mortality. Patients on maintenance dialysis are unique in the frequency in which they encounter healthcare settings. They are at the highest risk of contracting COVID-19 and have high mortality from the disease. Many changes have been made to their care in consideration of this.

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Authors

Ankur D. Shah, MD, Alpert Medical School of Brown University, Providence, RI; Division of Kidney Disease and Hypertension, Rhode Island Hospital; Division of Nephrology, Medicine Service, Providence Veterans Affairs Medical Center, Providence, RI.

Nathan Calabro-Kailukaitis, MD, Alpert Medical School of Brown University; Division of Kidney Disease and Hypertension, Rhode Island Hospital, Providence, RI.

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Correspondence

Nathan Calabro-Kailukaitis, MD
Division of Kidney Disease and Hypertension
375 Wampanoag Trail
East Providence, RI 02915.
401-649-4060
Fax 401-649-4061
Nathan.Calabro-Kailukaitis@Lifespan.org

Kidney Transplantation and COVID-19

BASMA MERHI, MD; REGINALD GOHH, MD

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INTRODUCTION

Kidney transplantation is the treatment of choice for patients with advanced chronic kidney disease or end stage kidney disease. More than 1,500,000 people live with a transplanted organ worldwide. In the United States, approximately 40,000 patients received an organ transplant in 2019 with almost 60% of those receiving a kidney transplant.[1] Generally, kidney transplant recipients receive induction therapy (antithymocyte globulin, basiliximab or alemtuzumab) at the time of transplant, followed by a maintenance immunosuppressive protocol consisting of prednisone, a calcineurin inhibitor (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus), and an antimetabolite (mycophenolic acid, azathioprine). Long-term immunosuppression is associated with an increased risk of infectious complications and specifically, transplant recipients are more susceptible to infections resulting from ribonucleic acid respiratory viruses.[2]

The enduring epidemic outbreak originating in Wuhan, China in December 2019 caused by the 2019 novel coronavirus (COVID-19) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created a dangerous and deadly public health disaster of international proportions. Although this outbreak has raised great concern among the general population, its specific impact on transplant recipients is unknown. The Centers for Disease Control and Prevention (CDC) lists immunocompromised patients, including those requiring immunosuppression following renal transplantation, as at high-risk for developing severe disease from COVID-19.

WHY KIDNEY TRANSPLANTATION SLOWED DOWN OR STOPPED DURING THE PANDEMIC

Due to the "uncertainty" of patient outcomes within the transplant community, transplantation volumes declined during the early period of the COVID-19 pandemic. In early April of this year, the United Network for Organ Sharing (UNOS) released data showing that transplantation rates in the US dropped sharply coincident with the timing of stringent infection control measures. There was a 51.1% reduction in deceased donor kidney transplantation and 71.8% of centers placed a complete suspension of live donor kidney transplantation.[3] Furthermore, 84% of transplant centers added stringent restrictions included transplanting only highly sensitized patients, those with a negative crossmatch, higher acuity patients and those without dialysis access.[3] Some centers reported transplanting only healthier recipients with the best quality organs and with the lowest risk of delayed graft function because of fears of overwhelming the health-care system that was already being stretched thin by the pandemic. Because of concerns of the sensitivity of the RT-PCR test and the fear of transmitting COVID-19 from the donor to the recipient, the decision to proceed with transplantation was made on a case-by-case basis, after careful assessment of the risks and benefits of transplantation. For this reason, rates of deceased donor discard and waiting list inactivation increased dramatically while the rate of new additions to the waiting list decreased during the pandemic. Using data from the National Organ Procurement Agency in France and the UNOS in USA, Loupy et al. showed that the trend in declining transplant rates accelerated over time from February 2020 until April 2020, with the reduction driven primarily by kidney transplantation. There was a 90.6% overall reduction in deceased donor kidney transplantation in France and 51.1% in the USA during this time period, although a substantial negative effect was also seen for heart, lung and liver transplants.[4] An analysis of US registry data showed that between March 15 and April 30, 2020, the numbers of deceased donor and live donor kidney transplant procedures were, respectively, 24% and 87% lower than would be expected based on pre-epidemic data.[5]

HOW TO MANAGE IMMUNOSUPPRESSIVE MEDICATIONS IN KIDNEY TRANSPLANT RECIPIENTS (KTRS) INFECTED WITH COVID-19

Because of their chronically immunosuppressed status, KTRs are at increased risk for infectious complications, accounting for significant morbidity and mortality. Infections rank as the second leading cause of death in these individuals.[6] Additionally, KTRs frequently suffer from medical conditions such as diabetes, hypertension, cardiovascular disease and chronic kidney disease that have been identified

as risk factors for adverse outcomes from COVID-19.[7] However, little is known about the true risk, presentation, and outcome of COVID-19 in KTRs. Furthermore, the optimal management of a solid organ transplant recipient with COVID-19 is not clearly determined. Reducing immunosuppression may not only lead to acute rejection but may result in an immune reconstitution-like reaction with paradoxical worsening of the infection.

Early reports of outcomes in kidney transplant patients with COVID-19 originated in Europe since the pandemic spread from Wuhan to this continent before spreading to the rest of the world. These are limited predominantly to case series and single-center studies and are lacking in control groups of non-transplant patients. Regardless, observational studies can provide useful early insights into effective treatment strategies. Alberici et al[8] described the early experience of COVID-19 infections among 20 Italian KTRs. Management consisted of the withdrawal of all immunosuppression followed by the administration of hydroxychloroquine (95%), lopinavir/ ritonavir (79%) and the administration of methylprednisolone (16 mg) in all patients. Additionally, six patients who deteriorated clinically were given tocilizumab. In this limited cohort, the development of COVID pneumonia was associated with a high risk of clinical deterioration. ICU level care was required in 20% of patients accompanied by a high rate of acute allograft injury (30%) and a mortality rate of 25%. The UK experience was summarized by Banerjee et al,[9] describing the clinical course of 7 KTRs infected with COVID-19. Modifications in the immunosuppressive regimen consisted of withdrawal of the antimetabolite and reducing the tacrolimus dose, while prednisone was kept unchanged or increased. 57% of patients required ICU admission and were otherwise managed with supportive care alone. In this cohort, older and diabetic patients were at higher risk for poor outcomes, with elevate D-Dimer, ferritin and troponin levels clinically predictive of case severity. In their series, 57% of patients developed acute kidney injury with mortality rate of 14%.

In early March of this year, New York City became the epicenter of the coronavirus pandemic in the United States. At Montefiore Medical Center, Akalin et al[10] summarized the course of 36 KTRs with COVID infection during the outbreak in New York City between March 16 and April 1, 2020. Seventy-five percent of affected individuals were recipients of deceased donor kidney transplants and maintenance immunosuppressive regimen consisted of tacrolimus, MMF and prednisone. Most patients suffered from medical comorbidities including hypertension (94%), diabetes (69%), a history of smoking or active smokers (36%) and heart disease (17%). Management consisted of the withdrawal of the antimetabolite in most patients (86%) and tacrolimus (21%) in severely ill patients. Eighty-six percent of patients received hydroxychloroquine and 2 patients received tocilizumab. Allograft outcomes were poor with 21% of patients requiring renal replacement therapy. The study showed a high early mortality rate of 28% at 3 weeks. In another study from New York during the first three weeks of the outbreak (March 13 to April 3, 2020), Pereira and colleagues described the outcomes of COVID-19 infections in ninety patients with solid organ transplants which included 46 KTRs.[11] Many patients had comorbidities associated with COVID-19 severity, such as obesity, cardiovascular disease, and chronic kidney disease. Seventy six percent required hospitalization and 35% required mechanical ventilation. As per previous studies, immunosuppressive medications were reduced (88% antimetabolite, 7% steroid and 18% CNI decreased or held). Ninety-one percent of patients received hydroxychloroquine, 66% azithromycin, 3% remdesivir, 21% tocilizumab, and 24% bolus steroids. The overall mortality rate was 18%. Twenty-four percent of hospitalized patients and 52% of those who were admitted to the intensive care unit died during the 3-week study period.

The outcome of COVID-19 in elderly transplant patients was described by Crespo et al.[12] From March 12 until April 4, 2020, COVID-19 was diagnosed in 16 of 324 KT patients aged ≥65 years old (4.9%) in their cohort. Up to 33% showed renal graft dysfunction with short-term fatality rate of 50% at a median time of 3 days following admission. Those who died were more frequently obese, frail, and had underlying heart disease. The study is alarming for the early and high mortality rate among the elderly kidney transplant population infected with COVID-19.

WHAT IS THE ROLE OF TOCILIZUMAB AND REMDESIVIR IN TREATING KTRS WITH COVID-19?

As the cytokine storm triggered by the coronavirus may be responsible for severe manifestations of COVID-19, immunosuppressive therapy could potentially mitigate some of these effects and reduce the risk of developing complications. Therefore, interleukin-6 (IL-6) targeting therapies have been proposed to manage the acute respiratory distress syndrome and organ dysfunction when present. Perez-Saez et al[13] published their multicenter cohort experience using tocilizumab, a monocolonal antibody directed against the IL-6 receptor, in 80 KTRs in Spain with COVID-19. The mortality rate was high at 32.5% with a predilection for older patients (> 60 YO). Of note, 10% of treated patients developed superimposed bacterial infection after tocilizumab infusion. IL-6 and other inflammatory markers, including LDH, ferritin, and D-dimer increased early after tocilizumab administration and correlated with poor patient survival. CRP was the only marker that decreased within 72 hours after tocilizumab administration and was associated with improved outcomes. The authors found no difference in respiratory improvement at 72 hours following Tocilizumab infusion between survivors and non-survivors. Non-survivors were more severely ill at presentation and

received tocilizumab more frequently in the intensive care unit. The authors concluded that declining CRP levels after tocilizumab administration together with clinical and radiological response might help to identify patients with favorable outcomes. In contrast, 2 case reports describing the use tocilizumab in 2 KTRs infected with COVID-19 showed rapid resolution of the cytokine storm and favorable clinical course without the need of mechanical ventilation[14,15], suggesting that earlier treatment in the disease course may be beneficial. Larger randomized controlled trials are clearly needed to confirm the utility and safety of Il-6 inhibition in treating KTRs with COVID-19.

Remdesivir is a nucleoside analogue prodrug that has been shown to have inhibitory effects on pathogenic animal and human coronaviruses, including COVID-19 in vitro. On May 1, 2020, the Food and Drug Administration (FDA) issued an emergency use authorization for this anti-viral agent for treatment of severe COVID-19 patients. The preliminary results of a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with COVID-19 have recently been published, documenting faster recovery time (11 vs 15 days) and reduced mortality by 14 days in the treatment arm.[16] To date, no similar trials have been conducted in solid organ recipients and its value in treating COVID-19 in this cohort remains to be determined.

CASES AT RHODE ISLAND HOSPITAL

The Transplant Program at Rhode Island Hospital (RIH) experienced 16 kidney transplant recipients infected with COVID-19 between March 1 and May 18, 2020. Of these, three had previously failed their allografts with return to renal replacement therapy, although all remained on immunosuppressive therapy at the time of infection. All three were subsequently taken off their immunosuppression following confirmed infection and did well without hospital admission or additional adjunctive therapy. Of the 13 active KTRs infected with COVID-19, 2 patients transplanted more than 10 years previously were managed as outpatients and 11 KTRs required hospitalized. The median age of the cohort was 54 years with the majority being female (62%). Immunosuppressive medications were reduced in 12 of 13 patients by discontinuation of the antimetabolite followed by a reduction in the calcineurin inhibitor dose. Interestingly, tacrolimus or sirolimus levels were noted to be supratherapeutic in 67% of patients on hospital presentation, which was likely due to increased drug absorption from COVID-induced diarrhea or decreased drug metabolism resulting from hepatic dysfunction. Adjunctive therapy consisted of remdesivir (36%), convalescent plasma (46%) and tocilizumab (27%). IL-6 levels were markedly elevated (>1,000) in 3 KTRs. There was a single mortality, involving the only patient treated with hydroxychloroquine. Of note, hydroxychloroquine was not commonly used at RIH as a treatment regimen while extremely elevated levels of IL-6 were common compared to the other studies. All 3 patients who received tocilizumab survived with one patient developing superimposed bacterial infection with graft pyelonephritis and ESBL bacteremia. Convalescent plasma was well tolerated in the four patients treated and subsequent publications have since shown that convalescent plasma could help patient recovery from COVID-19,[17-19] prompting emergency use approval by the FDA as a potential treatment option.

CLINICAL OUTCOMES

Current reports suggest that kidney transplant recipients show similar symptoms but worse outcomes when compared to the general population. Indeed, results from the TANGO International Transplant Consortium from the US, Italy and Spain identified 144 hospitalized adult kidney transplant recipients infected with COVID-19 and showed high rates of acute kidney injury (51%) and mortality (32%) among this cohort with non-survivors being older and having higher Il-6 levels.[20] This outcome is similar to previous single-center reports discussed here, which observed death rates between 14% and 30%. Of note, this and previously published studies focusing on solid organ transplant patients lacked comparison with a control group to ascertain their risk as compared to a general population. To address this knowledge gap, Molnar and colleague compared outcomes in solid organ transplant (SOT) recipients versus non-SOT patients with COVID-19 who were admitted to intensive care units throughout the US, using data from a multicenter cohort study.[21] Using a propensity score-matched cohort, the authors showed that death within 28 days of ICU admission was similar in SOT and non-SOT patients (40 and 43% respectively, respectively) and showed that there was no difference between groups in the duration of ICU length of stay, risk of ARDS, secondary infection, thromboembolic events, or receipt/duration of invasive mechanical ventilation. The authors suggested that the higher use of corticosteroids treatment in SOT compared to non-SOT patients may have contributed to this favorable outcome. Furthermore, they hypothesized that immunosuppressive medications may have mitigated pro-inflammatory cytokine activation in SOT patients, which might result in a lower risk of developing cytokine-release syndrome.

CONCLUSIONS

As the COVID-19 pandemic continues to progress, we are likely to see an increasing number of kidney transplant recipients who will be exposed to and subsequently develop a COVID-19 infection. However, the current management of COVID-19 disease in kidney transplant recipients remains ill-defined. No randomized controlled trials have

been conducted to assess how immunosuppression should be managed during acute infection nor how they should be resumed after remission. COVID-19 is associated with a higher mortality rate in KTRs than the general population with particularly poor outcomes noted in elderly kidney transplant population. Given the high mortality rate, transplant clinicians should focus on primary prevention with a careful case-by-case assessment of risk versus benefits of continuing immunosuppression in those infected. It seems rational to reduce the immunosuppressive load with first step being the withdrawal of antimetabolite agents followed by a reduction or discontinuation of the calcineurin inhibitor. Several agents have been used for treating KTRs infected with COVID-19 although none have shown proven efficacy. Ultimately, studies with a larger number of patients and longer follow-up are required to better assess the optimal management, outcomes, and treatment of kidney transplant recipients with COVID-19 infection.

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Authors

Basma Merhi, MD, Division of Kidney Transplantation, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

Reginald Gohh, MD, Division of Kidney Transplantation, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

Correspondence

Basma Merhi, MD
APC 921, 593 Eddy Street
Providence, RI, 02903
401-444-8431
bmerhi@lifespan.org