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.

References

1. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3**(5): 1526-33.
2. US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2019.
3. CMS. Preliminary Medicare COVID-19 Data Snapshot. https://www.cms.gov/files/document/medicare-covid-19-data-snapshot-fact-sheet.pdf (accessed 8/11/2020.
4. Dialysis Clinic I. COVID-19 Update from Dr. Doug Johnson. https://www.dciinc.org/wp-content/uploads/2020/08/COVID-19-DCI-Update-8.9.20.pdf (accessed 8/11/2020.
5. Fisher M, Yunes M, Mokrzycki MH, Golestaneh L, Alahiri E, Coco M. Chronic Hemodialysis Patients Hospitalized with COVID-19 – Short-term Outcomes in Bronx, New York. *Kidney360* 2020: 10.34067/KID.0003672020.
6. Valeri AM, Robbins-Juarez SY, Stevens JS, et al. Presentation and Outcomes of Patients with ESKD and COVID-19. *J Am Soc Nephrol* 2020; **31**(7): 1409-15.
7. Ma Y, Diao B, Lv X, et al. COVID-19 in hemodialysis (HD) patients: Report from one HD center in Wuhan, China. *medRxiv* 2020: 2020.02.24.20027201.
8. Xiong F, Tang H, Liu L, et al. Clinical Characteristics of and Medical Interventions for COVID-19 in Hemodialysis Patients in Wuhan, China. *J Am Soc Nephrol* 2020; **31**(7): 1387-97.
9. Alberici F, Delbarba E, Manenti C, et al. A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection. *Kidney Int* 2020; **98**(1): 20-6.
10. Centers for Disease Control and Prevention. Interim Additional Guidance for Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed COVID-19 in Outpatient Hemodialysis Facilities. https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis.html.
11. Centers for Disease Control and Prevention. Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the Coronavirus Disease 2019 (COVID-19) Pandemic. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html. Accessed August 15, 2020.
12. Rombola G, Heidempergher M, Pedrini L, et al. Practical indications for the prevention and management of SARS-CoV-2 in ambulatory dialysis patients: lessons from the first phase of the epidemics in Lombardy. *J Nephrol* 2020; **33**(2): 193-6.
13. La Milia V, Bacchini G, Bigi MC, et al. COVID-19 Outbreak in a Large Hemodialysis Center in Lombardy, Italy. *Kidney Int Rep* 2020; **5**(7): 1095-9.

14. Cho JH, Kang SH, Park HC, et al. Hemodialysis with Cohort Isolation to Prevent Secondary Transmission during a COVID-19 Outbreak in Korea. *J Am Soc Nephrol* 2020; **31**(7): 1398-408.
15. Dudreuilh C, Kumar N, Moxham V, Hemsley C, Goldenberg S, Moutzouris DA. De-isolation of COVID-19-positive hemodialysis patients in the outpatient setting: a single-center experience. *Kidney Int* 2020; **98**(1): 236-7.
16. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. *J Am Soc Nephrol* 2020; **31**(7): 1384-6.
17. Barlow A, Landolf KM, Barlow B, et al. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. *Pharmacotherapy* 2020; **40**(5): 416-37.
18. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report. *N Engl J Med* 2020.
19. Dirk M, Hentschel AKA, Jeffrey H. Lawson for the American Society of, the DaINAatVASo, (VASA) A. Maintaining lifelines for ESKD patients - ASDIN and VASA joint statement.
20. Ronco C, Manani SM, Giuliani A, Tantillo I, Reis T, Brown EA. Remote patient management of peritoneal dialysis during COVID-19 pandemic. *Perit Dial Int* 2020; **40**(4): 363-7.
21. Srivatana V, Liu F, Levine DM, Kalloo SD. Early Use of Telehealth in Home Dialysis during the COVID-19 Pandemic in New York City. *Kidney360* 2020; **1**(6): 524-6.
22. Wilkie M, Davies S. Peritoneal Dialysis in the time of COVID-19. *Perit Dial Int* 2020; **40**(4): 357-8.

Acknowledgment

AS and NC are supported by research and educational grants from Brown Physicians Inc and the Rhode Island Hospital Department of Medicine Chairs Research and Educational Programs.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs or the United States government.

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.

Financial Disclosure

The authors declared that they have no relevant financial interests.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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