Updates on Hemodialysis

Chapter 1

COVID-19 in Chronic Hemodialysis Patients

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Abstract

Coronaviruses are a group of mRNA viruses that may cause diseases in mammals and birds. Human coronaviruses may cause mild to moderate upper respiratory tract illnesses, and the first novel coronavirus strain was discovered in the 1960s as being responsible for some cases of the common cold in humans. In 2003, another novel coronavirus strain was discovered to affect the upper and lower respiratory tracts, causing severe acute respiratory syndrome (SARS) in humans and becoming known as SARS-CoV. In 2012, another novel strain was discovered to be responsible for many reported cases of severe respiratory illness in the Middle East before spreading to other countries, and it became known as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The most recent novel strain emerged in 2019 (dubbed Coronavirus Disease 2019 or COVID-19) and quickly spread to become a major global health burden. This chapter will discuss the available data about COVID-19 in patients with end-stage renal disease (ESRD) receiving chronic hemodialysis (HD).

Keywords: Hemodialysis; Chronic dialysis; COVID-19; Coronavirus 2; SARS-CoV-2.

Introduction

Coronavirus disease 2019 (COVID-19) is an illness that is caused by a novel coronavirus calledsevere acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. This virus was first discovered in Wuhan, China, in 2019 as being responsible for a cluster of cases of atypical pneumonia [2]. However, it then spread rapidly to other countries, and on March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [1]. Patients with end-stage renal disease (ESRD) are at increased risk of acquiring COVID-19 and are more susceptible to severe disease and poor outcomes [3-5]. There are several factors that may contribute to these increased susceptibilities. For example;

- High burden of co-morbidities, such as ischemic heart disease and diabetes, in patients with ESRD on dialysis [5-7].

- Patients receiving in-center HD have a more difficult time practicing social distancing because they have to go to their dialysis facilities three times a week, during which they are in contact with other patients and health care providers, as well as in contact with other people while traveling to and from their dialysis facilities. The importance of this point was supported by retrospective data, which showed that undergoing dialysis at home was associated with a lower probability of being infected with COVID-19, and other data observing a low incidence of symptomatic COVID-19 in peritoneal dialysis (PD) patients with a rate close to that of the general population [7, 8].

- The immunocompromised state of HD patients, which increases susceptibility to infections and, as a result, the risk of mortality and morbidity [9]. For a better understanding of this point, we need to remember the two lines of defense of the natural immune system against viral infections [10]. The first is the innate immune system, which is considered to be non-specific and the first defense line of the body (for example, the innate lymphocytes, natural killer cells, macrophages, etc.). The second is the adaptive or acquired immune system that is more specific and develops as a second line of defense (for example, the T- and B cells produced from lymphoid organs) in response to exposure to a pathogen [10]. In 2020, Ma et al reported some early data from China, which showed that HD patients with COVID-19 have much lower levels of immune cells (like killer T-cells and T and B cells) and cytokines compared to patients with COVID-19 who are not on dialysis and also compared to dialysis patients without COVID-19. This suggests that HD patients have a compromised immune system and are unable to mount a robust immune response to COVID-19.

Epidemiology

As of December 2022, more than 600 million confirmed cases of COVID-19 have been reported all over the world with more than 6 million cases of death [11]. The frequency of CO-

VID-19 varies from country to country, and may vary according to the region within a specific country. For example, the interactive real time web-based dashboard that was developed by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University to track COVID-19 indicates that there have been more than 4.5 million confirmed cases of COVID-19 in Canada with an incidence rate of 11,779 per 100,000 people over a 28-day period [12]. While in the United States (USA), there have been more than 100 million confirmed cases with an incidence rate of 30,580 per 100,000 people over the same time period [12]. Within the United States, the rate of reported cases per 100,000 people varied between different states and between different cities within a state over a specific time period [13]. The frequency of COVID-19 among patients with ESRD receiving chronic HD also varies between regions, but is overall higher than the general population of every specific region [14]. For example, the prevalence of COVID-19 among adult patients receiving chronic HD at around 1300 dialysis facilities across the USA as reflected by the presence of SARS-CoV-2 antibodies ranged from zero to 33.6% according to the state with an average of 8.35% [15]. In the United Kingdom (UK), the seroprevalence of SARS-CoV-2 antibodies in patients receiving in-center HD was 22.2% (16). When using a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay as the screening tool, data from dialysis units in France showed that 19% of chronic HD patients had COVID-19 [3].

Clinical Presentations

Given the fact that patients on HD have an altered immune system response to infections as explained before, they may also have different clinical presentations, risk factors, and outcomes compared to the general population. Even among patients on HD, the severity and spectrum of the clinical manifestations may vary according to patients' demographics and comorbidities, the region or country where COVID-19 is contracted, the variant of COVID-19, the wave or timeline of the COVID-19 pandemic, and the vaccination status of affected patients.

Asymptomatic

In general populations, asymptomatic infections are a well-known presentation of COVID-19 with variations in the reported rate, and based on a meta-analysis involving a large number of populations with COVID-19, the rate of asymptomatic infection among confirmed cases is around 40% [17]. In HD patients, the reported rate of asymptomatic COVID-19 infection confirmed by PCR testing ranged from 2 to 68% [4, 6, 7, 18, 19]. Using SARS-CoV-2 antibodies, data suggests a rate of 40.3%, similar to that seen in the general population [16]. The importance of this asymptomatic group is that it could be a potential source of infection for others or cause an outbreak in healthcare facilities like dialysis units, where the index case would likely be hard to identify. Furthermore, some asymptomatic HD patients had significant

laboratory and CT chest changes, indicating the presence of severe infection [20]. As a result, screening high-risk asymptomatic patients with NPS and CT chest is advised [20].

Symptomatic

Among those who are symptomatic, the spectrum of presenting symptoms and their severity may vary from individual to individual according to several factors. None of the COVID-19 symptoms is specific, and their frequency among HD patients with confirmed COVID-19, as suggested by several studies conducted across the world [3, 4, 6, 14, 18-27], is as follows:

- Cough: 7.1-83.9%
- Fever: 9-100%
- Shortness of breath: 0-64%
- Fatigue/Myalgia; 2.9-63%
- Gastrointestinal symptoms: 0-40%
- Sore throat: 0-20%
- Other symptoms like rhinorrhea and ageusia were less commonly mentioned in the studies.

Overall, fever, cough, and shortness of breath were less frequently reported in HD patients compared to the general population, while fatigue was more common [24].

The severity of COVID-19 has been classified by the National Health Commission of China according to the clinical presentations of cases into mild, moderate, severe, and critical [28].

- Mild cases: mild clinical symptoms with no evidence of pneumonia on chest radiology. Moderate cases: patients with fever and respiratory symptoms with chest radiology imaging suggestive of pneumonia.
- Severe cases: if the patient has any of the followings: shortness of breath, and respiratory rate of ≥ 30 breaths/min; resting SpO2 ≤ 93% on room air; PaO2/FiO2 ratio ≤ 300 mmHg, rapid progression of clinical symptoms, with lung lesions in chest radiology progressing at a rate of more than 50%.
- Critical cases: if the patient has any of the following: severe respiratory failure requiring mechanical ventilation; shock, or any other organ failure requiring intensive care.
- When applying these criteria to HD patients, some data found that 59% of cases were

mild/moderate, and 41% were severe or critical [24].

Laboratory Findings

In the right clinical settings and when resources are available, testing to confirm or rule out COVID-19 should be performed. Possible clinical scenarios may include:

- The presence of clinical features suggestive of COVID-19.

- Asymptomatic patient with a positive history of contact with a case of COVID-19, recent travel to an epidemic area, during an outbreak in a dialysis facility, and/or prior to certainprocedures. In the event of COVID-19 contact, the Centers for Disease Control and Prevention (CDC) recommends testing at least 5 days after the contact [29].

The diagnosis of COVID-19 infection is confirmed by detection of SARS-CoV-2 RNA using nucleic acid amplification tests (NAATs) such as reverse transcription-polymerase chain reaction (RT-PCR), or by detection of viral protein using an antigen test. These tests are not affected by the patient's vaccination status. Serological tests are used to detect circulating antibodies from previous infections or vaccinations. Some of the serological tests do not distinguish between prior infection and prior vaccination, while others do. Table 1 summarizes the general types of COVID-19 tests. The choice between tests may depend on several factors including the purpose of testing, the pre-test probability, the type of test available, the potential shortage of testing resources, how quickly the results are needed, etc. [29].

Many HD facilities use PCR testing for COVID-19; however, sometimes more rapid results are needed for many possible reasons. For example, to determine the need for performing dialysis in an isolation room when COVID-19 is suspected, when facility staff is suspected to have COVID- 19, or when screening patients during an outbreak. The role of rapid antigen testing as a preventive measure for the spread of COVID-19 in a HD facility has been evaluated, and rapid antigen testing was able to detect less than one-third of all infected patients. Additionally, it was also unable to detect COVID-19 during the incubation period of the illness in a small proportion of patients who became symptomatic a few days after the screening [30]. There is a scarcity of data comparing how different diagnostic tests perform in HD patients to the general population.

Despite that, and despite the fact that SARS-CoV-2 testing using on-site point of care NAATs or antigen tests are not as sensitive as those performed in laboratories [29], they should be considered by HD facilities for rapid identification of cases whenever possible. Isolation and all measures to prevent an outbreak could then be planned and implemented according to the results.

In the general population, hospitalized patients with COVID-19 infection commonly

have lymphopenia (with variable changes in the total White Blood Cells (WBC) count, high level of inflammatory markers (e.g. C-Reactive Protein (CRP), procalcitonin, and ferritin), high aminotransaminase levels, high lactate dehydrogenase (LDH), and abnormal coagulation profile,including D-Dimer [22,32]. Although HD patients may not be able to mount the same level of inflammatory response seen in the general population with COVID-19, some data from HD facilities across the world indicate that HD patients with COVID-19 may also present with significant lymphopenia, high inflammatory markers, high LDH, and high D-dimer [3,6,18,20,33].

Radiological Findings

In the general population, many patients with COVID-19 present with abnormal chest X-rays (CXR), despite that, CXR still has a lower sensitivity than initial RT-PCR testing for COVID-19 (69% versus 91%, respectively) [34]. In a small percentage of patients, CXR abnormalities may precede positive RT-PCR [34]. Chest computed tomography (CT) is more sensitive than CXR, and the detection of COVID-19 using chest CT is very high among symptomatic individuals [35]. The most common abnormalities seen on chest imaging are bilateral ground glass opacities and consolidation involving the bilateral lungs in a peripheral distribution [34, 35]. Among HD patients with COVID-19, CXR and chest CT are also commonly abnormal with bilateral ground glass opacities being the most common finding [3,4,6,18,19,21,23,25-27,33].

Risk Factors for Adverse Outcomes

Although the majority of COVID-19 patients have mild to moderate disease, some may develop severe illness that necessitates hospitalization, an intensive care unit (ICU), and/or mechanical ventilation. In general, HD patients have higher pulmonary infectious mortality rates compared with the general population [36]. The rate of COVID-19-related mortality in general population may vary according to patient-related factors, the timeline in the course of COVID-19, the predominant variant of the virus, and geographical factors [37]. Patients on chronic HD are at much higher risk of death from COVID-19 compared to general population (30% to 130% risk of death, with mortality rates ranging from 16% to 32% [24, 38, 40, 41]. Some have suggested that this higher risk of death is probably explained by the higher risk of endothelial dysfunction in HD patients due to their uremic milieu and altered immune system [24]. The median time from admission to death is 6 to 14 days, and the median time from symptoms to death is 7 to 17 days [15, 22, 26]. The main causes of death are presumed to be mainly from cardiovascular disease and respiratory distress syndrome [21,24]. A systematic review of COVIC-19 data in HD patients found that the hospitalization rate ranged from 35% to 88%, the median length of stay ranged from eight to 25.5 days, and the rate of ICU admissions ranged from 2% to 70%, with a median length of 13-15 days [14]. Like in the general

population, certain factors have been associated with increased risk of mortality and other adverse outcomes:

Patients-related factors

• Age: COVID-19 could affect individuals of any age group; however, older patients are more likely to have a severe infection [39]. In fact, Age is the strongest risk factor for severe COVID- 19 outcomes in general population, with risk increasing progressively and markedly with increasing age [37]. Among HD patients, age has also been shown to be one of the predictors of mortality in many studies conducted in different countries across the world [4, 6, 7, 23, 26, 40, 41].

• Gender: In the general population, it has been observed that males are at higher risk of serious outcomes including death [42, 43]. Although there is a tendency toward a higher risk of mortality among HD males with COVID-19 compared to females, the difference did not reach statistical significance in most of the studies [19, 21, 23-27, 33].

• Race and ethnicity: White/non- Hispanics have the highest risk of death and other adverse outcomes in general population, followed by Hispanic/Latinos, and then Black and non- Hispanics [44]. Asians and non-Hispanics are at lower risk of infections and adverse outcomes [44]. Data on the effect of race or ethnicity on mortality risk in HD patients is scarce and c contentious. Some data suggest that a Black/non-Hispanic background was associated with a lower risk of death; other data suggest the opposite, while some other data found no difference among different races or ethnic backgrounds [4, 21, 41, 45, 46].

• Comorbidities: many underlying medical conditions, like diabetes and cardiac diseases, have been associated with increased risk of adverse outcomes in patients with COVID-19 (39, 47). Data suggest that HD patients with a greater number of comorbidities (or a higher Charlson comorbidity score) are more susceptible to COVID-19 (25, 27, 33), but some comorbidities like diabetes and cardiac diseases have been associated with a higher mortality rate [7, 24, 26].

• Severity of presenting clinical features: HD patients who had severe symptoms at time of diagnosis and required hospital admission [6], and/or had hypoxemia at time of presentation [24, 26] are more likely to die.

• Laboratory markers: thrombocytopenia, prolonged baseline activated partial thromboplastin time [26], hypoalbuminemia [7, 24], anemia [24], higher WBC [25], high inflammatory markers (LDH, procalcitonin, and CRP [25, 33] in HD patients with COVID-19 are probably associated with a higher mortality rate.

Geographical and temporal factors

When comparing observed and predicted monthly number of deaths among HD patients dialyzing in different facilities in the United States, geographic and temporal patterns of excess mortality have been observed [48]. The variation in the reported rate of death according to the county has also been noted [4, 6, 24, 25].

COVID-19 Variants

SARS-COV-2, like other viruses, constantly change through genetic mutations, and new variants may develop. Although these variants may share many of the original virus's properties, they may also differ in terms of transmissibility, response to available therapies and vaccines, and disease severity. For example, since the initial waves of COVID-19–related deaths in 2020 and early 2021, which coincided with widespread transmission of the first SARS-CoV-2 variants in the United States, two additional waves of COVID-19–related deaths have occurred, coinciding with the emergence of new genomic variants (Delta and Omicron) [37]. At the end of 2021 and into 2022, sub-variants of Omicron emerged [37]. The timeline of these waves has been divided by the CDC into periods according to the predominant circulating variant of SARS-COV-2 (e.g., Delta, Early Omicron, Later Omicron, and Omicron BA.5). The number of COVID-19–related deaths during the later Omicron period and continuing into the BA.5 and later subvariant periods was relatively low compared to the large number of COVID-19–related deaths that occurred during the Delta and early Omicron periods [37].

Other factors

Some additional factors like (late referral to the hospital, late initiation of steroids [26], and staying at a nursing home, have also been associated with an increased mortality rate [26, 45].

Prevention

Prevention of COVID-19 should include: vaccination, appropriate structural and functional modifications of the dialysis facility to ensure social distancing, education of patients and healthcare providers, strict screening and surveillance plans, and strict implementation of infection control policies.

Vaccination

Vaccination remains one of the most effective tools for fighting many infectious diseases and minimizing their health and economic burdens. During pandemics, access to vaccines is usually prioritized, taking into consideration multiple factors including the risk of acquiring the disease, the risk of serious outcomes based on patients' risk factors, the amount of the avail-

able vaccine, and its safety and efficacy profiles. COVID-19 vaccine is also the most effective measure to protect against severe illness or death. The CDC adopted the recommendations of the Advisory Committee on Immunization Practices (ACIP), which suggest two category groups to prioritize patients for COVID-19 vaccination [49]. The first group includes Group 1a (healthcare personnel and long-term care facility residents), Group 1b (frontline essential workers, persons aged ≥ 75 years), and Group 1c (persons aged 65-74 years, persons aged 16–64 years with high-risk medical conditions, and essential workers not recommended for vaccination in Phase 1b). The second group involves all people over the age of 16 who have not previously been recommended for vaccination. Chronic HD patients fall into group 1c because of their high-risk medical condition. However, different nephrology societies, like the International Society of Nephrology, call for higher prioritization of dialysis patients worldwide [38], and moving them up to group 1a.

The rationale behind this call is explained by the fact that patients receiving in-center HD have to visit their dialysis centers three times a week, during which they are in close contact with health care providers as well as other patients, resembling the risk faced by residents of long-term care facilities currently classified as group 1a. This is in addition to their higher risk of acquiring the disease and developing adverse outcomes, including death, compared to other groups currently classified as 1c (i.e., patients with other comorbidities like diabetes, obesity, etc.) [38].

Several COVID-19 vaccines have been developed around the world, and hundreds of vaccines are still in the pre-clinical phase of development [50]. In general, vaccine platforms are either whole virus vaccines (inactivated or live attenuated), or viral component vaccines (for example;

mRNA vaccines, vector virus vaccines, recombinant protein vaccines, and DNA vaccines). For COVID-19, some examples of the most commonly known vaccines are [50]:

mRNA vaccines: Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273)

- Vector virus vaccines: Janssen/Johnson & Johnson (Ad26.COV2.S), AstraZeneca (Ch-AdOx1nCoV-19/AZD1222), Sputnik V (Gam-COVID-Vac)
- Recombinant protein vaccines: Novavax (NVX-CoV2373)
- Inactivated vaccines: Sinopharm (BBIBP-CorV/HB02), Cinovac (CoronaVac).

The efficacy of COVID-19 vaccine in HD patients has been demonstrated in many clinical trials,which showed that COVID-19 vaccination would induce the generation of antibodies against SARS-COV-2 [51-57]. The reported seroconversion rate in these trials varied between 31% and 98%, which was observed around 3 weeks after vaccination. Previous COVID-19

infection, hemodiafiltration, being younger, and having a higher serum albumin level are all independent predictors of higher antibody levels [51]. However, some data suggest that the generation of anti- SARS-CoV-2 antibodies in HD patients is attenuated compared to healthy controls [57,58], and the antibody titer declines earlier over time when compared to general population [59]. Patients on chronic HD with lower serum albumin and longer dialysis vintages are more likely to have absent or attenuated responses to vaccination [57]. The clinical effectiveness of COVID-19 vaccines in HD patients has been demonstrated by many clinical trials, which showed a reduced risk of severe COVID-19 infection, reduced rate of hospitalization and death [58,60-62]. For example, the Ashby et al study has shown that two-dose COVID-19 vaccination was associated with a 75% lower risk of hospitalization and an 88% lower risk of death among HD patients compared with unvaccinated HD patients [61]. These benefits were still observed with time post vaccination, even in patients who were older than 65 years, and regardless of the vaccine type [61].

Most of the data available about the effectiveness of vaccines in HD patients are on mRNA vaccines [52-54, 58, 63, 64], and fewer data are available on other types of vaccines [54-56]. In fact, some studies observed a greater efficacy in preventing infection and death with the BNT162b2 vaccine compared with the CoronaVac (42.6% vs. 15.0% and 90.4% vs. 64.8%, respectively) [58]. Additionally, data comparing the mRNA-based BNT162b2 vaccine with adenovirus-based AZD1222 vaccine in dialysis patients suggest that the former induced higher titers of SARS-CoV-2-neutralizing antibodies compared to adenovirus-based AZD1222 vaccine. Moreover, the adenovirus-based AZD1222 vaccine was associated with significantly lower neutralizing antibody responses against variants such as the Delta variant compared with healthy controls [63]. Overall, the safety profile of COVID vaccines in HD patients is favorable [52, 55, 57]. No serious adverse events have been reported, and observed adverse events include fatigue, myalgia, low fever, pain at the site of injection, and headache.

In short, COVID-19 vaccination is effective and associated with significant clinical effectiveness in chronic HD patients. Chronic HD patients should have high priority access to vaccination. If options are available, mRNA vaccines are favored for chronic HD patients until more data are available. When using mRNA vaccines, you may use the dosing suggested for immunocompromised patients and give three doses of monovalent as a primary vaccine series for patients older than 12 years [64]. Wait 21 days between the first and second dose, and 28 days between the second and third dose. It is usually given intramuscularly in the deltoid muscle. A booster dose of a bivalent vaccine is recommended two months after the last dose of the primary series [64]. However, vaccination schedules should be individualized according to the availability of the vaccine, type, age, tolerance to previous doses, and other factors. The CDC suggests that the primary series be completed with the same vaccine. If this is not possible, the CDC recommends giving the second dose at least four weeks after the first. If two

different vaccine products are used to complete the series, no additional doses of a COVID-19 vaccine are recommended [64]. At this time, antibody testing to determine the response to vaccination or identify a prior infection is not recommended [64]. Individuals with a recent COVID-19 infection whether before or after the vaccine, need to continue their vaccine series after recovering from the acute infection. Waiting for two to three months after the infection is reasonable [64].

Social Distancing and Education

Social distancing was and is still a key element in controlling the spread of COVID-19 infection. In fact, a lockdown or "stay-at-home" order was implemented by the governments of several countries at certain points during the COVID-19 crisis. Schools, malls, restaurants, concert halls, and many other places were closed. Travel was banned, in-person group meetings were cancelled, and elective and non-urgent hospital procedures were postponed. Additionally, outpatient clinics were closed, and whenever possible, virtual clinics were implemented. The aim was to impose social distancing and try to curb the spread of COVID-19 infection. Chronic HD patients, on the other hand, have no choice but to attend their dialysis facilities in order to receive their scheduled dialysis sessions. Therefore, dialysis facilities need to ensure that strategies are implemented to mitigate their increased risk of exposure [14, 65, 66]. Many medical societies (e.g. CDC, the European Renal Association– European Dialysis and Transplant Association, and societies from Italy and India) have provided guidance for dialysis facilities on how to implement the best preventative measures [65]. Although most recommendations by these societies are similar, some minor differences according to local practices and resources do exist [65].

Patients should be educated on how to practice social distancing during their time in the facility, as well as during other times when they are outside the facility. They should be aware of their increased susceptibility to acquiring the infection and their higher risk of developing adverse outcomes. They need to know that committing to social distancing at any time represents commitments to other patients and dialysis personnel too. This is because one person could be enough to cause an outbreak in the facility. If feasible, patients should use private transportation from and to the dialysis facility. Education must also include how to perform proper hand hygiene, the proper way of wearing a facemask, coughing and sneezing etiquettes, and what, when, and how to report symptoms to their dialysis centers. Dialysis facilities should use posters and signs at the entrances about COVID-19 with clear instructions on what to do and where to go. To avoid crowding, the arrival and departure times of each shift must be coordinated. Any updates or new knowledge related to COVID-19 should be shared with patients as well as dialysis personnel. Patients should receive psychological support when potential problems such as depression or anxiety are suspected. Education and support should also be provided to healthcare providers working in the HD facility. Providing frequent webinars to dialysis staff

should also be considered [65, 66].

Screening and surveillance

Patients with COVID-19 may be asymptomatic, or symptoms may appear 2-14 days after exposure. All people accessing the dialysis facility must be triaged and screened at the entrance for the most common symptoms of COVID-19, as well as the possibility of exposure to a COVID-19 patient. The dialysis facility must have a triage protocol for suspected patients. A suggested plan for dialysis facilities to mitigate the risk of COVID-19 is summarized in Figure-1. Having contingency and crisis plans in the event of outbreak is very important, and plans must address the possibility of an outbreak among dialysis nurses with the subsequent risk of a significant staff shortage. If dialysis-facility associated transmission of COVID-19 was suspected, screening tests of all patients and HCP of the same area and same shift should be performed. Expanding the testing depends on the number of identified cases, testing resources, and the likelihood of dialysis facility-associated transmission. Testing should be repeated every 3-7 days until no new cases are identified for at least 14 days [67]. Rincón et al described the result of screening asymptomatic patients in an outpatient dialysis facility after an outbreak, and 14 out of 170 (8.2%) asymptomatic patients tested positive for COVID-19 [68]. These patients were more likely to have shared health-care transportation to the dialysis unit, have been living in a nursing home, and have been admitted to the reference hospital within the previous 2 weeks [68].

According to resources and facility situation, some facilities may consider more frequent COVID testing or post-vaccination measurement of SARS-CoV-2-specific IgG to inform personalized vaccination schedules and use vaccine boosters if a low or waning IgG level is seen.

Infection Control and Personal Protective Equipment (PPE)

COVID-19 is generally spread by droplets expelled by coughing or sneezing. Fecal or direct- contact contamination may also occur. CDC does not require that patients with a suspected or infected COVID-19 infection be dialyzed in an airborne isolation room [69]. Ventilation systems in the facility need to be properly maintained. For all PPEs, dialysis facilities need to understand their PPEs inventory and utilization rate, and plan accordingly. The CDC has developed a personal protective equipment (PPE) burn rate calculator to help healthcare facilities know their consumption rate, estimate how long the remaining supply will last, optimize their current use of PPE and plan for future projected needs [70]. Facilities must have contingency strategies or plans to be used in addition to the conventional strategies if PPE shortage is anticipated. Additionally, crisis strategies need to be considered when the supply is not able to meet the facility's current or anticipated needs despite the implementation of conventional and contingency strategies [71]. Once PPE availability returns to normal, facilities need to resume conventional strategies. Conventional strategies may involve the use of physical barriers (e.g.,

glass or plastic windows at reception or triage area, curtains between patients), limiting the number of HCP not directly involved in patient care, limiting the number of visitors or caregivers accessing the dialysis facility to only those who are very important for the patients' safety and care, and cohorting patients and/or HCP whenever possible. All staff need to receive the required education and training on the proper utilization of PPEs. Conventional strategies for PPEs will also include:

Gloves and gowns: dialysis staff need to use FDA-approved disposable medical gloves and gowns when indicated, as per standard and transmission-based precautions. The situations when gloves and gowns are required or not need to be reviewed with the dialysis staff. For patients with suspected or confirmed COVID-19, dialysis staff should follow the standard contact and droplet precautions. The CDC does not recommend using more than one glove or gown at a time, when providing care to suspected or confirmed COVID-19 patients [71]. When the HD facility is short of PPE supplies, gloves and gowns should be prioritized for initiating and terminating dialysis, manipulating access needles and catheters, assisting patients to and from the dialysis station, and cleaning and disinfecting the dialysis station.

• Facemasks: facemasks are usually used by HCPs either to protect their nose and mouth when caring for patients, as per standard and transmission-based precautions, or to prevent the spread of any respiratory secretions when they are talking, sneezing, or coughing while they are in the facility. For the first purpose, facemasks should be removed and discarded after each patient encounter, however, they could be used until they become soiled or damaged when used for the second purpose. When indicated, FDA-cleared surgical masks should be used, and N95 masks should be saved for procedures that are likely to generate respiratory aerosols [71].

• Eye protection: dialysis staff should use eye shield or protection when caring for dialysis patients with suspected or confirmed COVID-19 infection. They could be either disposable (discarded after a single use) or reusable (should be cleaned and disinfected after each patient encounter according to the manufacturer instructions) [71].

In addition to the above, dialysis facilities need to continue their routine disinfection practices. For example, using disinfection wipes to clean dialysis machines, chairs, and equipment. The disinfection personnel need to wear the PPEs used for suspected or confirmed cases during the disinfection process, and they should ensure that all parts of equipment and dialysis chairs are wiped and allowed to air-dry [14]. Suspected or confirmed cases and any outbreak need to be reported to local health authorities according to local policies and procedures.

Pre-exposure Prophylaxis with EVUSHELD

EVUSHELD is a combination of two monoclonal antibodies (tixagevimab/cilgavimab), and it is authorized as pre-exposure prophylaxis to prevent COVID-19 in people who are mod-

erately to severely immune-compromised [72]. It can also be used by those for whom vaccination is not recommended, due to a history of severe adverse reaction to COVID-19 vaccination [72]. For eligible patients who can receive the vaccine, EVUSHELD is given to supplement the protection provided by the vaccine, and it is not meant to replace it. Dialysis patients are not currently listed by the CDC as immunocompromised patients eligible for EVUSHELD [72], and there is no published data about its use in HD patients. However, the CDC list is not intended to be an all- inclusive list, and clinical judgment must be used to determine if other patients are eligible or not. The current recommended dose is 300 mg of Tixagevimab plus 300 mg cilgavimab administered intramuscularly, and repeated every 6 months [72]. EVUSHELD could be less protective against certain variants, especially some Omicron sublineages, and clinicians should remain aware of variant prevalence in their specific region [72].

Management of Infected Patients

Dialysis-Related Management

- Fluid management: COVID-19 patients may lose weight for various reasons, especially during the early phase of infection. Therefore, it might be prudent to give careful attention to volume status, and consider reducing the target weight to improve the respiratory function [2].

- Circuit anticoagulation: Some patients may develop thromboembolic events, like dialyzer clotting and arteriovenous fistula thrombosis [3], therefore, heparin-free dialysis needs to be avoided, and increasing the dose of anticoagulant should be considered [3,14].

- Dialyzers: the use of high-efficiency dialyzers is suggested since many patients were considered in high catabolic states [14].

- Interaction with the HD nurse: direct interaction between the HD nurse and the patient during HD sessions should be limited as much as possible. Telemedicine interfaces with a camera should be used whenever possible to troubleshoot alarms from outside the room and to minimize the need to enter the room. Eating should not be allowed during the session to minimize time without mask, with exceptions to patients with confirmed hypoglycemia [14].

- The use of erythrocytes-stimulating agents (ESAs): the use of ESAs for the treatment of anemia in HD patients infected with COVID-19 is controversial. Some suggest that they should be avoided or limited because they could increase the prothrombotic risk posed by COVID-19 [73]. Others suggest that ESAs will not only improve anemia, but they may also have tissue protective antiapoptotic effects, and they may reduce the production of certain interleukins by monocytes and promoting regulatory T-cell survival [74].

- Dialysis-location and machines: Whenever possible, patients admitted to the ward should be isolated or cohorted with other COVID-19 patients. Dialysis could be performed in pa-

tients' rooms using portable machines, and the machines used for infected patients should be restricted in COVID-19 areas. Patients required admission to the ICU should be cohorted in dedicated isolation ICU rooms, and CRRT is preferred over conventional HD in this setting. Using extra-long tubing to allow the HD nurse to access machine outside the glass doors in ICU is recommended [75]. Prolonged intermittent renal replacement therapy (PIRRT) provides dialysis for an extended period (usually 6 - 18 h) with a higher flow rate, and can be used as an alternative to CRRT. One nurse could provide PIRRT to more than one patient at the same time, and the machine can be used for another patient in the same day [75].

Therapies for COVID-19

Like general population, symptomatic management with over-the-counter antipyretics or antitussives could be offered, with consideration for more specific measures for eligible patients. For example, antiviral therapy and anti-SARS-CoV-2 monoclonal antibodies should be considered in patients with mild-to-moderate COVID-19 who have risk factors for progression to severe COVID-19 [76]. Other lines of management (e.g. steroids, Janus kinase (JAK) inhibitor, interleukin-6 receptors antagonists, and antibiotics to cover for superimposed infection) should be considered for patients who need admission depending on the disease severity and the degree of requirement of oxygen supplementation [76]. There are no randomized controlled trials to study the outcomes of using these medications for HD patients with COVID-19.

In conclusion, HD patients are unique group of patients with regard to their risk of acquiring COVID-19 and their outcomes. Hemodialysis facilities need to adopt several strategies to mitigate the risk of COVID-19 among chronic HD patients. More studies about the effect of COVID-19 therapies in HD patients are encouraged.

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