Delivering Safe and Effective Hemodialysis in Patients with Suspected or Confirmed COVID-19 Infection: A Single-Center Perspective from Italy

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Introduction

New “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) is responsible for a clinical entity named Coronavirus Disease 2019 (COVID-19) by the World Health Organization, which is now a pandemic (1). In Europe, Italy was the first, and so far the largest, epicenter of the epidemic. It is now clear that many asymptomatic and paucisymptomatic patients went undetected, causing significant diffusion of the disease. Asymptomatic infections are common: among 634 confirmed patients on board the “Diamond Princess” cruise ship, 306 were symptomatic and 328 asymptomatic at the time of testing (2). It is now clear that when a patient with atypical severe pneumonia was diagnosed as COVID-19 in a small city, Codogno, in a previously healthy 38-year-old man, on February 20, 2020, more patients with undetected COVID-19 were present in Northern Italy. In addition to the cluster around Codogno, about 50 km south of Milan, which was promptly put under strict lockdown, two additional relevant clusters emerged near the cities of Bergamo and Brescia. The delay in enforcing a lockdown in the latter areas is probably one of the leading causes of the more severe outbreak now affecting these provinces. Extensive testing in the initial phase of disease diffusion was adopted in the Italian Veneto area, resulting in better containment of new cases. A nationwide lockdown measure was passed by the Italian government when Northern Italy, which has the highest concentration of well organized hospitals in the country, started showing signs of difficulty handling the rapid increase of patients in need of treatment in intensive care units (ICUs).

A comparison of Chinese and Italian data on COVID-19 may be of interest to other countries where the disease is now spreading. The Chinese Center for Disease Control and Prevention described the characteristics of a large cohort of COVID-19 patients (3), showing that 81% of patients experienced a mild disease (no or mild pneumonia), whereas severe or critical illness was reported for 14% and 5% of affected individuals, respectively. The overall patient fatality rate was 2.3%, although it was higher (14.8%) in patients aged >80 years. Mortality appears to be much worse in Italy, reaching up to 10%, although it is probably overestimated because many mild cases are undetected. The Italian Istituto Superiore di Sanità (Superior Health Institute) publishes and regularly updates a report describing the clinical characteristics of a tragically large cohort of people dying of COVID-19 (4). In total, 80% of deaths have occurred in three regions of Northern Italy: Lombardy, Emilia Romagna, and Piedmont. The median age of patients dying from COVID-19 infection is 80, with a larger proportion of men (67%). The median age of patients dying from COVID-19 infection in these regions is 18 years higher as compared with the nationwide sample diagnosed with COVID-19 infection, and 95% of deaths have occurred in people aged >60 years old. Among the most common comorbidities observed in COVID-19-positive deceased patients, CKD stage 3–5 was present in 23% of patients. After hospital admission, acute respiratory distress syndrome was observed in 97% of patients who eventually died. AKI was reported in 23.5% of patients. Superinfection was observed in 11% and acute cardiac injury in 10% of patients (4).

Handling Hemodialysis Patients with Suspected or Confirmed COVID-19 Infection

Dialysis patients are particularly predisposed to infections, which are their primary cause of morbidity and the second leading cause of death. Avoidance of infections in hemodialysis facilities through optimal infection control practices is critical for the safe management of dialysis patients, and the full use of recommended infection control guidelines is essential to prevent infections in this vulnerable population (5). Thus, dialysis nurses and doctors are already well prepared to handle the challenges posed by COVID-19, provided that they are well equipped and trained.

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Clinical Features and Diagnosis of COVID-19 in Dialysis Patients

Dialysis patients appear to have symptoms similar to those of the general population, but no studies to date have compared dialysis patients with the general population. Clinical features of COVID-19 may be present in other viral respiratory infections. Diagnosis can be strongly suspected on the basis of clinical findings, but it should be confirmed with a nasopharyngeal molecular test. However, a negative test in the presence of interstitial pneumonia does not exclude COVID-19, clinical findings being more reliable than the molecular test, which may yield a false negative. Fever, cough, fatigue, and myalgia are common both in mild and severe disease. Pneumonia can be diagnosed by chest imaging, typically showing bilateral infiltrates, although unilateral lung involvement is not unusual, or with bedside lung ultrasound.

Chinese investigators have proposed chest computed tomography (CT) scans as a gold standard for the radiologic diagnosis of COVID-19, showing a sensitivity of 98% (8), and have recommended its use for screening purposes, particularly when RT-PCR testing is negative. Still, lung ultrasound appears to be a reliable and more practical alternative (7). Lung ultrasound is useful for diagnosis in the general population, and it has several additional advantages: repeatability during follow-up, lower cost, easier patient management, and reduced need to use x-rays or CT scans. However, excess fluid in hemodialysis patients is frequent, and lung congestion is present in a high proportion of these patients, sometimes in the absence of symptoms (9). Thus, the diagnosis of COVID-19 pneumonia through lung ultrasound may be challenging in dialysis patients.

The symptoms most commonly observed at hospital admission of COVID-19 patients are fever, shortness of breath, and cough. It is essential to consider the following other symptoms that may be present at disease onset to clinically identify possible COVID-19 patients: fatigue, diarrhea, headache, muscle pain, chills, sweating, malaise, anosmia, ageusia, and hemoptysis (10). Rhinitis and sore throat are rare, occurring in <5% of patients. In some cases, only one or two of these symptoms occur in COVID-19-positive patients, which has consequences for controlling the disease in dialysis units. Blood tests are also relevant: lymphopenia has been reported to occur in 70% of patients, prolonged prothrombin time in 58%, and elevated lactate dehydrogenase in 40% (10). Severe cases have more often lymphopenia, hypoalbuminemia, higher levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer. Among cytokines, higher levels of IL-2R, IL-6, IL-10, and TNF-α have been reported (11).

The “Brescia Renal COVID Task Force” (12) divided hemodialysis patients into three groups on the basis of symptomatology, chest imaging, and severity of respiratory impairment (Table 1), with different management approaches.

Here, we provide our protocol for handling dialysis patients with suspected or confirmed COVID-19 infection. This protocol was derived from nephrology and dialysis Lombardy network discussions, and was previously published in part (12,13), with some modifications on the basis of internal guidance from our institution. Table 2 summarizes the sources of information available from the main scientific societies and government organizations in English-speaking countries. Naicker et al. (14) have reported and summarized COVID-19 guidelines for dialysis units developed by the Chinese Society of Nephrology and the Taiwan Society of Nephrology. Another useful publication comes from the European Dialysis Working Group of the European Renal Association – European Dialysis and Transplant Association (15). Thus, there is valuable advice for clinical nephrologists, but it is critical to adapt the information considering what can be achieved with locally available resources. If these are insufficient, patients should be referred to centers able to handle COVID-19 patients with advance agreements. However, because neighboring hospitals may also have a shortage of space and resources for infected patients, a contingency plan should be discussed with hospital administration in case there will be a large volume of hospitalized dialysis patients with COVID-19.

Pharmacologic treatments are not addressed, being a broad topic outside the scope of this article.

Protocol for Early Diagnosis of COVID-19 and Mitigation of Transmission in Dialysis Patients

The primary goal to keep in mind is to protect both patients and health care staff, through careful shielding of the dialysis unit from COVID-19 infection. In dialysis patients and the general population, COVID-19 may manifest with mild symptoms. Therefore, it is essential to screen and to isolate affected patients and staff.

- A dialysis team member contacts the patient or a trusted family member by phone to check for any changes in the patient's and family's health status. The telephone call occurs on the day before dialysis for the morning session, or in the morning of the same day for the afternoon/evening session.
- On the dialysis day, the patient arrives at the waiting room wearing a surgical mask, distributed during the previous dialysis session. In the waiting room, patients respect the minimum distance of 1 m. If the waiting room is too small, chairs can be placed in the corridors to avoid crowding. Drivers are requested to reduce or avoid transporting too many patients at the same time, which should be easy to do considering the low traffic during lockdown times.
Table 1. Choice of renal replacement therapy on the basis of the Brescia Renal COVID Task Force classification of hemodialysis patients affected by Coronavirus Disease 2019, with a positive swab molecular test

<table>
<thead>
<tr>
<th>Symptoms or Signs</th>
<th>Category One</th>
<th>Category Two</th>
<th>Category Three</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&lt;38°C</td>
<td>≥38°C</td>
<td>≥38°C</td>
</tr>
<tr>
<td>Dry cough</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Dyspnea with desaturation &lt;95%</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Bilateral infiltrates on chest x-ray</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Need for invasive ventilation</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Type of RRT</td>
<td>Outpatient HD in a dedicated area, if home quarantine is possible</td>
<td>Inpatient HD (dedicated area in the dialysis unit or 1:1 HD in the patient’s room)</td>
<td>CRRT</td>
</tr>
</tbody>
</table>

Category one: asymptomatic or mildly symptomatic patients; category two: severe symptoms and no invasive ventilation; and category three: critical illness requiring intensive care unit admission. Clinical classification in categories is on the basis of the report by Alberici et al. (12). HD, hemodialysis; CRRT, continuous renal replacement therapy.

- A staff member gives the patient a new mask. Before entering the dialysis room, the patient washes their hands and the arterio-venous fistula arm for at least 20 seconds, supervised by a nurse who also asks again for information about the patient's health (specific questions on fever, cough, sore throat, colds, diarrhea, or other significant symptoms, even if unrelated to the COVID-19 infection).
- After entering the corridor leading to the dialysis room, the patient performs hand rubbing with antiseptic gel.
- During the entire dialysis session, the patient wears a surgical mask. The same mask is kept for transportation back home.
- During the dialysis session, no snack is provided to avoid lowering the mask and to reduce personnel-patient contact. Furthermore, blankets, which are difficult to wash frequently, are banned and only cotton sheets are provided.
- At the end of the dialysis session, the patient has to wash her/his hands before going home.
- Patient transport to and from the dialysis unit is a crucial aspect of COVID-19 infection prevention (12). Transport providers may have difficulties in providing their services, especially if transportation is done with ambulances, which may be required for members of the general population with COVID-19. In addition, it is preferable that the number of patients transported simultaneously is reduced. Drivers should protect themselves and also take care to avoid exposure of dialysis patients to the virus, by wearing a surgical mask and by periodic, accurate disinfection of their vehicle. If available during lockdown times, relatives can help by driving their loved ones to the dialysis unit.

Management Protocol for Suspect Cases

If there is suspicion of COVID-19 at initial screening, axillary temperature, O₂ saturation with a disposable digital oximeter, and BP are assessed. The nephrologist then decides whether to send the patient to the hospital “COVID Emergency Room." If this is the case, the patient is accompanied as potentially COVID-positive, wearing a surgical mask and gloves. In the Emergency Room, the molecular test for SARS-CoV-2 (swab), a chest x-ray, and laboratory tests are done.

Because it takes at least 7 hours to get the results of the swab test in our center, the patient may need dialysis before knowing the result. Even for patients who develop symptoms on nondialysis days and are directed to the Emergency Room after telephone interview, test results may not be available before a scheduled dialysis session. Thus, while waiting for the swab result, patients undergo dialysis in an isolated room with a dedicated nurse equipped with adequate protection. Because there are false-negative results, for patients with a negative first swab, a second swab test is taken and the patient remains isolated. In the event of two negative tests, clinical assessment is critical before returning the patient to the regular dialysis room, because suspicion of COVID-19 may remain strong if typical pneumonia is present at x-ray or pulmonary ultrasound. In such cases, a pulmonary CT scan may help.

Management Protocol for Confirmed Cases

Patients with confirmed COVID-19 infection have different management protocols on the basis of the severity of the clinical picture (Table 1).

- Patients are not hospitalized, but should be isolated from other people who could be infected, including relatives. If home isolation is not possible, such as in the case of many family members living in a small house, patients should ideally stay in dedicated COVID-19 buildings offered by health authorities (hotels or deliberately prepared structures). This approach has been incredibly challenging in Italy and, in most cases, it has not been possible to implement it.
- Patients come to the hospital for dialysis either in their car or in an ambulance driven by professional drivers equipped with personal protective equipment (PPE). During the ambulance journey, patients wear surgical masks and gloves. The driver disinfects the vehicle after each trip.
- Patients undergo dialysis in an isolated area with an independent entrance and dedicated dialysis machines. The dedicated dialysis unit was derived from an area in a nearby nephrology unit, initially with a single station and later expanded to five stations. Two doors for isolating this area were constructed. The osmosis water distribution ring was expanded. A filter zone for the undressing of staff exiting the COVID-19 area was established. Each dialysis
unit should look for the best possible solution to isolate COVID-19 patients. There are many possible options, from transferring patients to other COVID-19-enabled units to dedicating shifts to COVID-19-positive patients. The latter solution, which has been applied in Italian units located in areas with extremely high prevalence of the disease because other options were unavailable, poses a higher risk of COVID-19 transmission to other patients and staff.

- At the end of dialysis treatment, the room is cleaned and disinfected, and the dialysis machine undergoes standard sterilization. Careful disinfection practices, including disinfection wipes for the dialysis machine, chair, and all dialysis station surfaces and equipment, are performed.

**Category Two: Symptomatic Patients Requiring Hospital Admission, without the Need for Invasive Respiratory Support**

- Dialysis patients in this group need hospitalization. They may eventually recover or progress to severe respiratory insufficiency, and the need for invasive ventilation may ensue. Dialysis patients often have several concomitant comorbidities. In Italy, the median age at the start of dialysis is 70 years. Thus, it is likely that dialysis patients may be considered too compromised to survive high-pressure invasive ventilation and may therefore not be regarded as adequate candidates for intubation. However, dialysis patients can survive COVID-19, and nephrologists should be their advocates, discussing the individual patient with the intensivist in charge of the decision to proceed to mechanical ventilation. **Dialysis per se** is not an exclusion criterion, but the overall prognosis should be considered, keeping in mind that some patients have the prospect of kidney transplantation or can survive over 30 years of dialysis treatment.

- Patients in group two may need continuous positive airway pressure treatment. Consequently, moving them to the dialysis unit can be complicated. In our hospital, we have created two dialysis stations, each into two negative pressure rooms in the infectious diseases department, with one dialysis machine each, which are used for our patients with COVID-19. Each room has a portable osmosis unit, after urgent setup of an adequate water hookup. Standard bicarbonate dialysis is the most straightforward approach. Dialysis machine sterilization is performed as usual at the end of the hemodialysis session. Proper external disinfection is mandatory.

- As COVID-19 is characterized by a prothrombotic state, be aware of an increased risk of vascular access thrombosis.

**Category Three: Patients with Respiratory Insufficiency Requiring Intensive Care**

This category of patients will be receiving mechanical ventilation. Hemodialysis in this complex setting is difficult to perform, but it is a possible option. Continuous RRT (CRRT) is preferable, and it is
commonly used for COVID-19 patients developing AKI. Alternative approaches could be adopted, such as the hybrid therapies known as prolonged intermittent RRT or sustained low-efficiency dialysis (SLED), using conventional hemodialysis machines with lower blood-pump speeds and dialysate flow rates. If CRRT or hemodialysis machines are scarce, urgent-start peritoneal dialysis (PD) could be an option. It has been proposed in natural disaster scenarios and other crisis situations, where it could be the only available life-saving dialysis modality for AKI (16). PD may be challenging to operate when patients are prone, and the intra-abdominal dialysis fluid may impede respiration, but previous experience has shown that it is a possible approach (17). An essential issue for hemodialysis patients admitted to the ICU is the type of vascular access for CRRT. In case they have an arteriovenous fistula or graft, should they get a central venous catheter to avoid prolonged needle cannulation? Because long term CRRT may be associated with accidental needle disconnection, some would prefer placing a new central venous catheter. Dialysis-specific plastic cannulae may be helpful in this setting. On the other hand, a central line could favor vein thrombosis and infection. Central veins could also be not patent or already in use with other lines. Thus, an individual, case-by-case decision is warranted.

COVID-19 patients in our population

In the first 50 days of the Lombardy epidemic, we had 12 of 215 (5.6%) patients with COVID-19 among hemodialysis patients, none with PD. Only 1 of 12 patients probably contracted the infection within the dialysis unit. We also treated two patients coming from other dialysis centers, and we are dialyzing two previous CRRT patients discharged from the ICU who developed ESKD. Among the 16 treated patients, only 2 could remain at home because of low-level symptoms and the possibility of adequate isolation. Thus, the hospitalization rate was high (87%), but six category one patients were admitted despite minor symptoms because adequate home isolation was not possible. The remaining eight patients were category two, indicating a clinical need for hospitalization of 50%. Three of them, aged >80 years old, worsened to category three and died. None of them was considered for mechanical ventilation because of poor prognosis.

When to Resume Hemodialysis in an Outpatient Unit

The correct timing for the reintegreation of cured hemodialysis patients in regular dialysis centers is uncertain because, even after a negative swab test, patients could still be contagious for some time. Wang et al. (18) highlighted that in patients with confirmed COVID-19, nasal and pharyngeal swabs were negative in 37% and 68% of cases, respectively, highlighting the need for concomitant nasopharyngeal testing and the possibility of false-negative results. Chen et al. (19) reported several instances of SARS-CoV-2 detection in sputum or feces after pharyngeal swabs became negative.

In our hospital, the clinical definition of recovery is on the basis of three criteria: no fever, respiratory frequency <22 per minute, and O₂ saturation in ambient air >95%. After clinical improvement, patients must continue 2 weeks of dialysis treatment in the COVID-19 area. In the last days of isolation, two negative swab tests allow readmission to the regular dialysis center. If there is a shortage of swab tests, and it is not possible to obtain two negative samples before return to regular shift dialysis, one negative test can be accepted. Still, we suggest that even after 2 weeks without symptoms, patients should wear a surgical mask during dialysis because they still represent a low risk of diffusing the disease. One possible approach is also to group patients returning to regular dialysis treatment on the same shift.

Dialysis Prescription during the COVID-19 Emergency

Dialysis prescription has mainly been unchanged. We have seen an increased tendency toward dialysis circuit thrombosis and therefore a need for increased anticoagulation. For the same reason, some patients have switched from hemodiafiltration to bicarbonate hemodialysis. We were prepared to reduce treatment lengths or reduce dialysis frequency from three to two times per week in patients with residual renal function in case of extreme need, but this was not necessary.

Protection of Health Care Personnel

In Italy and several other countries, the number of infected health care personnel has been very elevated, reaching around 10% of the total number of infected individuals. The estimated number of health care personnel admitted to ICUs has also been elevated, at around 20% of the total number of infected individuals. Many have died.

Dialysis units are considered non-COVID-19 units, but patients and staff are forced to share a common space for hours. Thus, if a COVID-19 subject not yet identified is in the dialysis room, the chance of the infection spreading is high if inadequate protection is provided or if PPE is used inadequately. Dialysis nurses have extremely specific skills that require extensive training, and they are essential for providing dialysis treatment. A shortage of dialysis nurses could have catastrophic consequences on the management of dialysis facilities.

We try to give a high level of protection to dialysis staff (Figure 1), but this advice should be adapted to the overall availability of PPE in the specific area or hospital where the dialysis unit is located. Considering both nephrology and dialysis staff, we have observed 5 of 71 (7%) COVID-19 cases among nurses, and 1 of 15 (6.7%) cases among nephrologists and fellows. Overall, 86 people were exposed for 50 days to the potential contagion inside and outside the hospital, with COVID-19 incidence of 1.4 cases/1000 days of exposure.

Appreciation of the work done by dialysis nurses, who are under a lot of pressure, is more critical than ever. Do not underestimate the psychologic pressure on dialysis staff. It may not be as strong as that on ICU personnel dealing with the sickest patients with COVID-19, but fear of the disease and of transmitting it to their relatives is universal, and can determine burnout. In our hospital, the psychology department set up a telephone support service for health care personnel. Also, information regarding
to save the lives of patients and health care personnel. Units should be prepared to change their practice as needed of the pandemic changes in different countries. All dialysis that may be optimized as the clinical situation and burden main goal. Experience will aid the delivery of protocols a vaccine, mitigation of the outbreak must be the shared approach to dialysis in COVID-19 patients. Photo credit for Figure 1: developments and discoveries relating to COVID-19 in-fection, workplace risks, and self-protection should be shared within the unit: good communication is the best treatment for fear. It is not possible to predict developments in the current pandemic, but we know that we are facing the most severe health emergency since Spanish flu in 1918. While waiting for proven, effective treatments or a vaccine, mitigation of the outbreak must be the shared main goal. Experience will aid the delivery of protocols that may be optimized as the clinical situation and burden of the pandemic changes in different countries. All dialysis units should be prepared to change their practice as needed to save the lives of patients and health care personnel.

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Dialysis nurses provided valuable input in developing our approach to dialysis in COVID-19 patients. Photo credit for Figure 1: courtesy of Ms. V. Paonessa.

Author Contributions
M. Gallieni and D. Scorza were responsible for conceptualization; M. Gallieni and G. Sabiu were responsible for writing the original draft of the manuscript; M. Gallieni was responsible for writing the final version of the manuscript; and D. Scorza was responsible for writing revision.

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References
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