Delivering safe and effective hemodialysis in patients with suspected or confirmed COVID-19 infection: a single-center perspective from Italy

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The new “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) is responsible for a clinical entity named by the WHO Coronavirus Disease 2109 (COVID-19), which is now a pandemic (1). In Europe, Italy became the first and so far largest epicenter of the epidemic. It is now clear that many asymptomatic and paucisymptomatic cases went undetected, causing a significant diffusion of the disease. Asymptomatic infections are common: among 634 confirmed cases on board of the “Diamond Princess” cruise ship, 306 were symptomatic and 328 asymptomatic at the time of testing (2). It is now clear that when an atypical case of severe pneumonia was diagnosed as COVID-19 in a small city, Codogno, in a previously healthy 38 yo man, on Feb 20, 2020, more undetected cases had occurred in Northern Italy. In addition to the cluster around Codogno, about 50 kilometers 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 the disease diffusion was adopted in the Italian Veneto area, resulting in a 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 difficulties in handling a rapid increase of cases in need of ICU.

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 experimented a mild disease (no or mild pneumonia), while a severe illness and a critical illness were reported in 14% and 5% of affected individuals, respectively. The overall case-fatality rate was 2.3%, although higher, 14.8%, in patients aged >80 years. Mortality appears to be much worse in Italy, up to 10%, probably overestimated because many mild cases are undetected. The Italian Istituto Superiore di Sanità (Superior Health Institute) publishes and regularly updates a report describing clinical characteristics of a tragically large cohort of people dying of COVID-19 (4). 80% of deaths occurred in three regions of Northern Italy, Lombardy, Emilia Romagna, and Piedmont. The median age of patients dying for COVID-2019 infection was 80, with a larger proportion of men (67%). The median age of patients dying for COVID-2019 infection was 18 years higher as compared with the nationwide sample diagnosed with COVID-2019 infection, and 95% of deaths occurred in people >60 yo. Among the most common comorbidities observed in COVID-19 positive deceased patients, chronic kidney disease stage 3-5 was present in 23% of cases. After hospital admission, acute respiratory distress syndrome was observed in 97% of patients who
eventually died. Acute kidney injury was reported in 23.5% of cases. Superinfection was observed in 11% and acute cardiac injury in 10% of cases (4). Among critically ill patients referred for ICU admission in Lombardy, the majority were men (82%), with a median age of 63 years. A large proportion (88%) required mechanical ventilation. ICU mortality was 26%, and 16% were discharged, with the remaining 58% still treated in the ICU, indicating that overall mortality will be higher in the follow-up (5)

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 (6). 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.

Characteristics of the ASST Fatebenefratelli Sacco dialysis service, affiliated with the University of Milan, Italy.

Our academic nephrology and dialysis center operates in two public hospitals in Milan, one in the city center (Fatebenefratelli) and the other at the city border. Both serve heavily populated communities, with 23% of the general population older than 65 years. The “Luigi Sacco” hospital is a teaching hospital offering care in all specialties, and it is, in particular, a national reference center for epidemiological emergencies (SARS, Ebola, and bioterrorism), as well as for the diagnosis and treatment of infectious diseases. Overall, we treat 215 chronic hemodialysis patients and 45 peritoneal dialysis patients. Hemodiafiltration is performed in 50% of the hemodialysis population. The two nephrology wards have a total of 25 beds.

Clinical features and diagnosis of COVID-19 in dialysis patients.

Dialysis patients appear to have symptoms similar to the general population, but no studies compared the dialysis with the general population. Clinical features of COVID-19 may be present in other viral respiratory infections. Diagnosis can be strongly suspected based on clinical findings, but it should be confirmed with the 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 be 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, but unilateral lung involvement is not unusual, or with bedside lung ultrasound (7).

Chinese investigators proposed chest CT scans as a gold standard for the radiological diagnosis of COVID-19, showing a sensitivity of 98% (8) and 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 the 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, fluid excess 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. Other symptoms that may be present at the onset are essential to consider to clinically identify possible COVID-19 patients: fatigue, diarrhea, headache, muscle pain, chills, sweating, malaise, anosmia, ageusia, hemoptysis (10). Rhinitis and sore throat are rare, occurring in less than 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 occurred 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 were reported (11).

The “Brescia Renal Covid Task Force” published a report on the ERA-EDTA webpage (12). They divided hemodialysis patients into three groups based on symptomatology, chest imaging, and severity of respiratory impairment (Table 1), with different management approaches.

We provide here our protocol for handling dialysis patients with suspected or confirmed COVID-19 infection. This protocol was derived from the nephrology and dialysis Lombardy network discussions, published in part (12, 13), with some modifications based on 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. Besides, Naicker et al. (14) report and summarize 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 EUDIAL Working Group of ERA-EDTA (15). Thus,
there is valuable advice for the clinical nephrologists, but it is critical to adapt the information on what can be achieved with the locally available resources. If these are insufficient, patients should be referred to centers able to handle COVID-19 patients with advanced agreements. However, because the neighboring hospitals may also have a shortage of space and resources for infected patients, a contingency plan should be discussed with the hospital administration in case there will be a large volume of hospitalized dialysis patients with COVID-19.

Pharmacological 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 the healthcare staff, though careful shielding of the dialysis unit from the COVID-19 infection. In dialysis patients, COVID-19 may manifest with mild symptoms. It is, therefore, 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 one meter. 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 more patients at the same time, which should be easy to do considering the low traffic during lockdown times.
- A staff member gives the patient a new mask. Before entering the dialysis room, the patient washes hands and the AVF 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 hands rubbing with antiseptic gel.
- During the entire dialysis session, the patient wears a surgical mask. The same mask is kept for the transport back home
- During the dialysis session, no snack is provided to avoid lowering the mask and to reduce personnel to patient contact. Furthermore, blankets, which are difficult to wash frequently, were 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 service, especially if the transport is done with ambulances, which may be required for the COVID-19 emergency of the general population. In addition, it is preferable to reduce the number of patients transported simultaneously. Divers should protect themselves but also be careful in avoiding virus exposure of dialysis patients, by wearing a surgical mask and by periodic, accurate disinfection of their vehicle. If available during lockdown times, relatives could help by driving their loved ones to the dialysis unit.

Management protocol for suspect cases

If there is a suspicion of COVID-19 at the initial screening, axillary temperature, O2 saturation with a disposable digital oximeter, and blood pressure are detected. 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 ER, the molecular test for SARS-CoV-2 (swab), a chest X-ray, and laboratory tests are done.

Because the response of the swab takes at least 7 hours in our center, the patient may need dialysis before knowing the result. Even in patients who develop symptoms in the non-dialysis days and who are directed to the ER after the telephone interview, test results may not be available before the 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, in case of a first negative swab, a second swab is repeated, keeping the patient isolated. With two negative tests, clinical assessment is critical before returning the patient to the regular dialysis room, because COVID-19 suspect may remain strong if typical pneumonia is present at X-rays or pulmonary ultrasound. In these selected cases, a pulmonary CT-scan may help.

Management protocol for confirmed cases

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

Category 1, asymptomatic or mildly symptomatic patients.
- Patients are not hospitalized, but they should be isolated from other people who could be infected, including relatives. If home isolation is not possible, such as in the case of more family members living in small houses, patients should ideally stay in dedicated COVID buildings offered by health authorities (hotels or purposely prepared structures). This approach has been very challenging in Italy, and in most cases, it was not possible to implement it.
- Patients come to the hospital for dialysis either with their car or with an ambulance led by professional drivers equipped with 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. This dedicated dialysis unit was derived from an area of the nearby nephrology unit, initially with a single station, and later expanded to 5 stations. Two doors for isolating this area were constructed. The osmosis water distribution ring was expanded. A filter zone for the undressing of the staff exiting the COVID-19 area was predisposed. Each dialysis unit should look for the best possible solution in isolating COVID-19 patients. There are many possible options, from transferring patients to other COVID-19 enabled units to dedicating shifts to positive patients. The latter solution, which was applied in Italian units located in areas with a very 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 2: 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 yo. Thus, it is likely that dialysis patients may be considered too compromised to survive high-pressure invasive ventilation and, therefore, not regarded as adequate candidates for intubation. However, dialysis patients can survive COVID-19, and nephrologists should be their advocates, discussing the individual case with the intensivist in charge of the decision of proceeding 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 (CPAP) treatment. Consequently, moving them to the dialysis unit can be complicated. In our hospital, we created two dialysis stations, each into two negative pressure rooms of the infectious diseases department, with one dialysis machine each, used for our COVID patients. Each room has a portable osmosis unit, after an urgent setup of the adequate water hookup. Standard bicarbonate dialysis is the most straightforward approach. Dialysis machine sterilization is performed as usual at the end of the HD session. Proper external disinfection is mandatory.

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

Category 3, patients with respiratory insufficiency requiring intensive care.

This group of patients is under mechanical ventilation. Hemodialysis in this complex setting is difficult to perform, but it is a possible option. CRRT is preferable, and it is commonly employed for COVID-19 patients developing AKI. Alternative approaches could be adopted, such as the hybrid therapies known as prolonged intermittent renal replacement therapy (PIRRT) 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 AKI (16). PD may be challenging to operate when patients are pronated, and the intra-abdominal dialysis fluid may impede respiration, but previous experience showed 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 AV 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 infections. Central veins could also be not patent or already used with other lines. Thus, an individual, case by case decision is warranted. COVID-19 cases in our population

In the first 50 days of the Lombardy epidemic, we had 12/215 (5.6%) COVID-19 cases among hemodialysis patients, none in PD. Only 1/12 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 ESRD. Among the 16 treated patients, only two could
remain home because of low symptoms and the possibility of adequate isolation. Thus, the hospitalization rate was high, 87%, but six category 1 patients were admitted despite minor symptoms because adequate home isolation was not possible. The remaining 8 patients were category 2, indicating a clinical need for hospitalization of 50%. Three of them, aged over 80 yo, worsened to category 3 and died. None of them was considered for mechanical ventilation because of poor prognosis.

When to resume HD in an outpatient unit

The correct timing for the reintroduction of cured HD 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 confirmed COVID-19 patients, 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 the sputum or feces after pharyngeal swabs became negative.

In our hospital, a clinical definition of recovery is based on three criteria: no fever, respiratory frequency < 22/mi, and O₂ saturation in ambient air >95%. After clinical improvement, patients must continue two 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 could be accepted. Still, we suggest that even after two 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 grouping patients returning to the regular dialysis treatment on the same shift.

Dialysis prescription during the COVID-19 emergency

Dialysis prescription was mainly unchanged. We saw an increased tendency towards dialysis circuit thrombosis and, therefore, the need for increased anticoagulation. For the same reason, some patients switched from hemodiafiltration to bicarbonate hemodialysis. We were prepared to reduce treatment lengths or reducing 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 is very elevated, about 10% of the total amount of infected individuals. The estimated number of those admitted to the ICU is also elevated, 20% of the infected. Many 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 spreading infection is high if inadequate protection is provided or if PPE is used inadequately. Dialysis nurses have very specific skills that require extensive training, and they are essential for providing dialysis treatment. A shortage of dialysis nurses could have a catastrophic consequence 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 observed 5/71 (7%) COVID 19 cases among nurses and 1/15 (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 a COVID-19 incidence of 1.4 cases/1000 days of exposure.

Appreciation of the work done by the dialysis nurses, who are under high pressure, is more critical than ever. Do not underestimate the psychological pressure on the dialysis staff. It may not be as strong as that of ICU personnel dealing with the sickest COVID-19 patients, but fear of the disease and of transmitting it to their relatives is universal, and it can determine burnout. In our hospital, the psychology department set up a telephone support service for healthcare personnel. Also, information developments and discoveries on COVID-19 infection, workplace risks, and self-protection should be shared within the unit: good communication is the best treatment of fears.

Conclusions
It is not possible to predict developments in the current pandemic, but we know we are facing the most severe health emergency since the Spanish flu in 1918. While waiting for proven, effective treatments or a vaccine, mitigation of the outbreak must be the shared main goal. Experience helps in delivering protocols that may be optimized as the clinical situation and the burden of the pandemic changes in different countries. All the dialysis units should be prepared to change their practice as needed to save patients’ and healthcare personnel’s lives.
Acknowledgments

Dialysis nurses provided valuable input in developing our approach to dialysis in COVID-19 patients. Photo credits (figure 1): courtesy of Ms. Veronica Paonessa, RN.

Disclosures

The authors have nothing to disclose.

Author Contributions

M. Gallieni: Conceptualization; Writing - original draft and final manuscript

G. Sabiu: Writing - original draft

D. Scorza: Conceptualization; writing revision
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Table 1. Choice of renal replacement therapy (RRT) based on the Brescia Renal COVID Task Force classification of hemodialysis patients affected by COVID-19, with a positive swab molecular test. Category 1: Asymptomatic or mildly symptomatic patients; Category 2: Severe symptoms, no invasive ventilation; Category 3: Critical illness requiring intensive care unit (ICU) admission. HD: hemodialysis; CRRT: continuous renal replacement therapy. (Clinical classification in groups based on Alberici et al., ref. 12)

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<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
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<tr>
<td><strong>Fever</strong></td>
<td>&lt; 38° C</td>
<td>&gt; 38° C</td>
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<tr>
<td><strong>Dry cough</strong></td>
<td>± ✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Dyspnea with desaturation &lt;95%</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Bilateral infiltrates on chest X-ray</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Need for invasive ventilation</strong></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>
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<tr>
<td><strong>Type of RRT</strong></td>
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Table 2. Resources for nephrologists on COVID-19 in dialysis. This list, in alphabetical order, is limited to the main websites in the English language.

<table>
<thead>
<tr>
<th>Entity</th>
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<tr>
<td>ASN - American Society of Nephrology</td>
<td>Nephrologists Transforming Dialysis Safety (NTDS) web page. <a href="https://www.asn-online.org/ntds/">https://www.asn-online.org/ntds/</a></td>
</tr>
<tr>
<td>ISN - International Society of Nephrology</td>
<td>Recommendations for the Novel Coronavirus 2019 Epidemic <a href="https://www.theisn.org/covid19/recommendations">https://www.theisn.org/covid19/recommendations</a></td>
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| The Renal Association - UK | • COVID-19: Information and guidance for renal professionals [https://renal.org/covid-19/](https://renal.org/covid-19/)  
Figure 1. Optimal protective gear for hemodialysis in COVID-19 patients. Photo credits: courtesy of Ms. Veronica Paonessa, RN.