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REVIEW

Management of Patients on Dialysis and With Kidney Transplantation During the SARS-CoV-2 (COVID-19) Pandemic in Brescia, Italy

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease (COVID-19), is a major pandemic challenging health care systems around the world. The optimal management of patients infected with COVID-19 is still unclear, although the consensus is moving toward the need of a biphasic approach. During the first phase of the disease (from onset of the symptoms up to 7–10 days) viral-induced effects are prominent, with the opportunity to institute antiviral therapy. In the second inflammatory phase of the disease, immunosuppressive strategies (for example with glucocorticoids or anticytokine drugs) may be considered. This latter stage is characterized by the development of progressive lung involvement with increasing oxygen requirements and occasionally signs of the hemophagocytic syndrome. The management of the disease in patients with kidney disease is even more challenging, especially in those who are immunosuppressed or with severe comorbidities. Here we present the therapeutic approach used in Brescia (Italy) for managing patients infected with COVID-19 who underwent kidney transplantation and are receiving hemodialysis. Furthermore, we provide some clinical and physiopathological background, as well as preliminary outcome data of our cohort, to better clarify the pathogenesis of the disease and clinical management.

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We describe our experience with managing patients with kidney disease during the current COVID-19 pandemic in Brescia City in the Lombardy region of Italy, with particular attention to patients undergoing dialysis and patients with renal transplantation.

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The Chinese Center for Disease Control and Prevention recently published the largest COVID-19 case series, which includes 44,672 cases. This study shows an overall mortality rate of 2.3%. Besides age (1.3% mortality in the 50–59 age group, 3.6% in the 60–69 age group, 8.0% in the 70–79 age group, and 14.8% in the ≥80 age group), the main risk factors are the presence of cardiovascular diseases (10.5% mortality), diabetes (7.3% mortality), chronic respiratory diseases (6.3% mortality), high blood pressure (6% mortality), and cancer (5.6% mortality).[1,2] In the Lombardy region, however, the disease seems to have much higher mortality rates than reported in China, and this led us

to investigate factors potentially responsible for this worse outcome.[3] The comorbidities associated with increased mortality during COVID-19 are common in patients with chronic kidney disease (CKD) and in patients undergoing renal replacement therapy with hemodialysis. There is a paucity of data on the risk factors and outcome of patients with kidney disease who are positive for COVID-19, including those receiving dialysis or who underwent a kidney transplantation. These groups of patients are unique in view of their immunosuppressed status. Reports from China suggest a less severe course of the disease in patients receiving dialysis, compared with patients who underwent a kidney transplantation, but also compared with patients without kidney disease.

Currently, Brescia and its province are the second largest Italian area affected after Bergamo (5317 cases as of March 23, 2020). A working group consisting of infective disease specialists and intensivists from Lombardy has developed a therapeutic protocol in patients with COVID-19 based on disease severity.[4] We have adapted this protocol to our patients receiving dialysis and who underwent a kidney transplantation. We also provide some logistics considerations resulting from our direct experience in the management of patient flows during the COVID-19 pandemic, as well as preliminary results of outcome in our population.

Logistic Considerations

Proper logistic planning is crucial in the management of this health emergency. The management of these patients makes it necessary to reconcile infection protocols (e.g., isolation), with needs that are intrinsic to our specialty (e.g., the need to move patients for hemodialysis). Our experience, although still limited, suggests a better outcome in patients who underwent a transplantation directly managed in a dedicated nephrology ward compared with the patients managed in other general COVID areas, and evaluated by the nephrologist only in consultation.

As a referral center, our division provides care to 1200 patients who underwent a transplantation, 400 patients receiving hemodialysis, and 70 patients receiving peritoneal dialysis. Because of the significant size of our patient population, we reorganized our wards to accommodate the surge of patients with COVID-19 with kidney disease. The particular logistics of our institution has allowed us to implement an efficient organizational model that included the creation of a dedicated COVID unit from a female ward.

From February 27–28, 2020, we created a dedicated COVID unit that was dialysis capable and subsequently admitted the first COVID-positive patient (who underwent kidney transplantation). On February 28, we adopted surveillance measures for outpatients undergoing hemodialysis, which were applied in a small triage area in the waiting room of the dialysis center: patients' body temperature was checked together with a brief anamnestic evaluation, alcohol-based hand sanitizer was dispensed, and surgical masks were provided. If the clinical suspicion of COVID-19 emerged, the patient was sent to perform specific testing. In case of urgency for dialysis treatment, this was performed in a room intended for suspected cases.

Table 1. Number of patients at the peak of the COVID pandemic

1st Floor				
Inpatients with COVID-19 infection receiving hemodialysis **17 beds**	Hemodialysis room for inpatients with COVID-19 infection	Hemodialysis rooms for inpatients who are negative for COVID-19	Dialysis room for inpatients with COVID-19 infection or suspected cases	Inpatients with COVID-19 who received transplantation **12 beds**
2nd Floor				
Dialysis				COVID-negative nephrology ward

COVID, coronavirus disease.

Between March 2 and 4, 2020, we admitted the second and third positive patients to the COVID area. As the number of patients infected with COVID-19 increased, we closed the transplant center and rearranged the ward's central spaces to create hemodialysis rooms, intended partially for patients with SARS-CoV-2 infection and partially for patients who are negative for SARS-CoV-2 (see Table 1).

Patient Flow

Logistical challenges and the physical structure of the building (e.g., identifying a room dedicated for isolated patients awaiting the reverse transcriptase-polymerase chain reaction results, locations for donning and doffing personal protective equipment, as well as for performing hemodialysis outside the usual area), we were forced to reduce the number of overall beds from 36 to 29. Because of patient turnover (intensive care unit transfers, discharges, and deaths), these numbers allowed us to cover our needs in terms of admissions for patients who underwent transplantation and who are receiving dialysis.

Up to March 22, in the nephrology unit of the hospital of Brescia, we have managed 46 patients, following the protocol presented in this article: 20 patients who underwent renal transplantation, 21 patients receiving hemodialysis, and 5 patients affected by CKD or acute kidney injury on CKD. The vast majority of patients (19 of 20 patients who underwent transplantation, 17 of 21 patients receiving hemodialysis, and 4 of 5 of the patients with CKD) received

antiviral therapy and hydroxychloroquine as per our protocol. Dexamethasone and tocilizumab have been used, respectively, in 11 and 6 of the 20 patients who underwent transplantation, in 4 and 1 of the 21 patients receiving hemodialysis, and in 1 and none of the patients with CKD. To date, no patients on immunosuppressive treatment due to primary or secondary glomerulonephritis have been admitted or known to have symptoms imputable to SARS-CoV-2 infection; these patients were advised to respect social distancing rules since the early stages of the coronavirus crisis.

Results

We now provide preliminary outcome data on the patients directly followed in our nephrology unit in Brescia on March 22, 2020; more detailed reports will follow. As of March 22, among our 20 patients who underwent transplantation who were admitted, 5 patients died, 4 were admitted to the intensive care unit, and 3 were discharged after an average of 13 days.

We admitted 21 patients with COVID-19 infection receiving hemodialysis, including 5 patients who died and 4 who were discharged between hospital day 7 and 17 (mean length of hospitalization 12 days). Of note, the COVID-19 crisis has imposed, at least at some stages, rationalization of intensive care unit resources.

A total of 5 patients with CKD were admitted, of whom 2 have died and the other 2 have been discharged after 6 and 17 days from admission.

Management Considerations

In general terms, optimal disease management is still being debated, and the therapeutic approach still lacks significant evidence. The indication for antiretroviral therapy is uncertain, and to date there are no approved drugs for the treatment of SARS-CoV-2 infection.[5] Although anecdotal experience can be drawn from the use of antiviral agents on viruses belonging to the same family of Betacoronaviruses (SARS and Middle East respiratory syndrome), the current COVID-19 pandemic requires the identification of effective therapies. To date, no clear guidelines exist for the management of these patients in general and for hemodialysis and transplant patients in particular.[6]

The pharmacological approach to treating SARS-CoV-2 infection can be viewed as a 2-phase approach. The first phase is associated with viral replication and cytopathic effect, and antiviral drugs may be considered (e.g., chloroquine-hydroxychloroquine, lopinavir/ritonavir, darunavir ritonavir, and darunavir/cobicistat). The second phase of the disease begins after 7 to 10 days from the onset of symptoms, and is associated with the risk of death[2]; this stage is characterized by progressive lung involvement with escalating needs of oxygen supplementation and ventilatory support, which seems to be secondary to hyperinflammatory and cytokine release syndromes. Immunosuppressive and immunomodulatory drugs may be of benefit during this phase.

Chloroquine-Hydroxychloroquine

Investigational evidence seems to support the role of antiviral activity of chloroquine toward the SARS and avian influenza viruses in *in vitro* and animal models.[7,8] Clinical evidence to support their use remains limited at this time.[9] Because of similar molecular structure, a well-known immunomodulating effect,[10] and better safety profile, hydroxychloroquine may be considered as an option in this context,[11] and of interest its use has been found to be associated with a higher proportion of patients showing a negative reverse transcriptase-polymerase chain reaction from day 3 after its introduction compared with untreated controls in small series.[12]

Lopinavir/Ritonavir, Second-Generation Antiretroviral

Anecdotal evidence seemed to support their possible role in COVID-19; however, a recent analysis failed in showing benefit with lopinavir/ritonavir treatment beyond standard care in hospitalized adult patients with severe COVID-19,[13] but these results are limited and, in our opinion, not conclusive. For example, baseline characteristics suggest a higher disease severity in the treatment arm (more patients with respiratory rate >24/min, with days from onset to randomization >12 and requiring oxygen) and, interestingly, an associated higher viral load. Despite that, patients treated with lopinavir/ritonavir experienced a higher proportion of clinical improvement on day 14 (45.5% vs. 30.0%), a shorter time to clinical improvement if treated within 12 days from onset (hazard ratio 1.25; 95% confidence interval: 1.77–2.05), and were less likely to die (19.2% vs. 25.0%, not significant). In our opinion, these data support consideration of antiviral therapy in subgroups of patients at high risk.

Darunavir Ritonavir and Darunavir/Cobicistat

These are potential alternatives to lopinavir/ritonavir based on the similar mechanism of action.

Remdesivir

Remdesivir is a nucleotide analogue whose mechanism of action consists of incorporating the drug into newly synthesized RNA chains. It has been suggested that it plays a role in reducing viral load and improving lung function parameters in animal and *in vitro* models,[14,15] acting at the stage of the post virus entry in the cells.[7]

Azithromycin

A small study performed on patients with COVID-19 infection and treated with hydroxychloroquine

demonstrated that combination with azithromycin was associated with a higher probability of showing a negative reverse transcriptase-polymerase chain reaction for the virus from the third day after the beginning of the therapy compared with controls and with those who received hydroxychloroquine alone.[12]

Corticosteroids

The use of corticosteroids would be contraindicated in the first phase of the disease, but may play a role in the second phase, the one characterized by potential rapidly progressive lung involvement and secondary to hyperinflammatory syndrome and cytokine release syndrome. Of note, data suggest a significant impact on the survival curves of patients with COVID-19 infection who have developed acute respiratory distress syndrome.[16]

Tocilizumab

In consideration of the central role that interleukin-6, in combination with other proinflammatory cytokines, seems to have in the development of the cytokine release syndrome,[17] tocilizumab could play a role in the management of selected cases in the absence of major contraindications.

Clinical Patient Management and Monitoring

Patients with known COVID-19 infection receive a chest X-ray at baseline and repeated when respiratory deterioration is noted. Even patients who are afebrile may have an abnormal chest X-ray and other clinical signs of the hemophagocytic syndrome. These patients tend to be hypercoagulable, and prophylactic therapy with heparin and low-dose aspirin should be considered. During this phase, treatment with glucocorticoid and the interleukin-6 inhibitor tocilizumab should be considered, especially in patients with rapid clinical deterioration evidenced by escalating oxygen requirements or the need for ventilatory support. We recommend for this subgroup of patients, close monitoring of arterial oxygen levels with repeat arterial blood sampling, of the blood tests including ferritin–coagulation–liver enzymes, and of the chest X-ray.

We have formulated a treatment protocol based on patient characteristics, phase of illness, and disease severity using antivirals, immunomodulators, and immunosuppressive agents. These protocols are based on *in vitro* antiviral effects and empirical observations in other countries and are listed in the Supplementary Appendix S1. A recent trial did not show efficacy of lopinavir-ritonavir in severe COVID-19 infection, although with the limitations mentioned previously; of note, data on the role of such approach on subgroups such as patients receiving hemodialysis and who underwent transplantation are still lacking. Our proposed therapeutic management plan for patients receiving hemodialysis and who underwent transplantation with a SARS-CoV-2 infection can be found in the Supplementary Appendix S1. We also provide further considerations for diagnosis and treatment of these patients in the Supplementary Appendix S2.

APPENDIX

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DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTAL MATERIAL

Supplementary File (PDF)

Appendix S1. Proposal for a therapeutic management plan for patients receiving hemodialysis and who underwent transplantation and who have a SARS-CoV-2 infection.

Appendix S2. Further considerations for diagnosis and treatment.

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