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Management Of Patients On Dialysis And With Kidney Transplant During SARS-COV-2 (COVID-19) Pandemic In Brescia, Italy

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Abstract

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 COVID-19 infected patients is still unclear, although the consensus is moving towards 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 anti-cytokines 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 haemophagocitic 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 employed in Brescia (Italy) for managing kidney transplant and hemodialysis patients with COVID-19. Furthermore, we provide some clinical and physiopathological background, as well as preliminary outcome data of our cohort, in order to better clarify the pathogenesis of the disease and clinical management.

Introduction

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 renal transplant patients.

The China CDC has recently published the largest COVID-19 case series, which includes 44,672 cases. This study shows an overall mortality rate of 2.3%. Beside age (1.3% mortality in the 50-59 age group, 3.6% in the 60-69 age group, 8% 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 haemodialysis. There is a paucity of data on the risk factors and outcome of COVID-19-positive patients with kidney disease – including those on dialysis or with kidney transplant. These groups of patients are unique in view of their immunosuppressed status. Reports from China suggest a less severe course of the disease in dialysis patients, compared to kidney transplant patients, but also compared to patients without kidney disease.

Currently, Brescia and its province is the second largest Italian area affected after Bergamo (5317 cases as of 23 March 2020). A working group consisting of infective disease specialists and intensivists from Lombardy has developed a therapeutic protocol in COVID-19 patients based on disease severity(4). We have adapted this protocol to our dialysis and kidney-transplanted patients. We will 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 make 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 haemodialysis). Our experience, though still limited, suggests a better outcome in transplant patients directly managed in a dedicated nephrology ward compared to 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 transplant patients, 400 haemodialysis and 70 peritoneal dialysis patients. Due to the significant size of our patient population we re-organized our wards in order to accommodate the surge of COVID-19 patients with kidney disease. The particular logistics of our institution has allowed us to implement an efficient organizational model which included the creation of a dedicated COVID unit from a female ward.

On 27-28 February, we created a dedicated COVID unit that was dialysis capable and subsequent admitted the first (kidney-transplant) COVID positive patient. On February 28th 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.

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

Patients flow

Logistical challenges and the physical structure of the building (e.g. identifying room dedicated for isolated patients awaiting for the RT-PCR results, locations for donning and doffing Personal Protective Equipment

(PPE) as well as for performing haemodialysis outside the usual area), we were forced to reduce the number of the overall beds from 36 to 29. Due to patient turnover (ICU transfers, discharges and deaths), these numbers allowed us to cover our needs in terms of admissions for transplant and dialysis patients.

Up to the 22nd of March, in the Nephrology unit of the hospital of Brescia we have managed 46 patients, following the protocol presented below: 20 renal transplant patients, 21 on haemodialysis and five affected by CKD or AKI on CKD. The vast majority of patients (19/20 transplant patients, 17/21 hemodialysis patients and 4/5 of the CKD patients) received antiviral therapy and hydroxycloroquine as per our protocol. Dexamethasone and tocilizumab have been employed, respectively, in eleven and six of the 20 transplant patients, in four and one out of the 21 haemodialysis patients and in one and none of the CKD patients. 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-2infection; these patients were advised to respect social distancing rules since early stages of the coronavirus crisis.

Results

We will now provide preliminary outcome data on the patients directly followed in our Nephrology unit in Brescia at the 22 of March 2020, more detailed reports will follow. As of march 22nd, among our 20 transplant patients admitted, 5 patients died, 4 were admitted to the ICU and 3 were discharged after an average of 13 days.

We admitted 21 hemodialysis patients with COVID-19 including 5 patients that has died and 4 that were discharged between hospital day 7 and 17 (mean length of hospitalization 12 days) . The COVID-19 crisis has imposed rationalisation of ICU resources and as a result, hemodialysis patients who are often elderly and afflicted by numerous comorbidities, are often not considered candidates who will benefit from ICU care.

A total of 5 patients with CKD were admitted, of whom, 2 have died and the other two 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 anti-retroviral therapy is uncertain and to date there are no approved drugs for the treatment of SARS-CoV-2 Infection(5). Although, anectodatal experience can be drawn from the use of antiviral agents on viruses belonging to the same family of Betacoronaviruses (SARS and MERS) the current COVID 19 pandemic provides the opportunity for testing therapies in affected patients. To date, no clear guidelines exist for the management of these patients(6).

The pharmacological approach to treating SARS-CoV-2 Infection can be viewed a two-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 begin after 7-10 days from the onset of symptoms onset and is associated with the risk of death(2); this stage is characterised by progressive lung involvement with escalating needs of oxygen supplementation and ventilatory support, which seems to be secondary to a 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 towards 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). Due to similar molecular structure, a well known immunomodulating effect(10) and better safety profile, hydroxycholoroquine may be considered as an option in this context(11) and of interest its use has been found as associated to a higher proportion of patients showing a negative RT-PCR from day 3 after its introduction compared to untreated controls in small series(12).

Lopinavir/ritonavir: second-generation anti-retroviral. 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 randomisation

>12 and requiring oxygen) and interestingly, an associated higher viral load. Despite that, patients treated with lopinavir/ritonavir experienced higher proportion of clinical improvement on day 14 (45.5%vs30%), a shorter time to clinical improvement if treated within 12 days from onset (HR1.25,95%CI 1.77-2.05) and were less likely to die (19.2%vs25%, not significant). In our opinion, this data support consideration of antiviral therapy in subgroups of patients at high risk.

Darunavir ritonavir and darunavir/cobicistat: potential alternatives to lopinavir/ritonavir based on the similar mechanism of action.

Remdesivir: nucleotide analogues whose mechanism of action consists in 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 hydroxycloroquine, demonstrated that combination with azithromycin was associated with a higher probability of showing a negative RT-PCR for the virus from the third day after the beginning of the therapy compared to controls and to those who received hydroxycloroquine 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 characterised 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 that have developed acute respiratory distress syndrome (ARDS)(16).

Tocilizumab: in consideration of the central role that IL-6, in combination with other pro-inflammatory 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 IL-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 the 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 anitiviral effects, empirical observations in other countries and listed in the supplement. A recent trial did not show efficacy of lopinavir-ritonavir in severe COVID-19 infection although with the limitations mentioned above; of note data on the role of such approach on subgroups such as haemodialysis and transplant patients still lack. Our proposed therapeutic management plan for haemodialysis and transplant patients with SARS-COV-2 infection can be found in the Supplemental Material. We also provide further considerations for diagnosis treatment of these patients in the Supplemental Material.

The Brescia Renal Covid Task Force

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Conflict of Interest

Authors declare no conflict of interest.

Supplemental Material

A. Proposal for a therapeutic management plan for haemodialysis and transplant patients with sars-cov-2 infection.
B. B. Further considerations for diagnosis and treatment.

Supplementary information is available at *KI Report's* website.

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

1st Floor:

COVID-19 HAEMODIALYSIS INPATIENTS **17 beds**	HAEMODIALYSIS ROOM FOR COVID-19 INPATIENTS	HAEMODIALYSIS ROOMS FOR COVID-19 NEGATIVE	DIALYSIS ROOM FOR COVID -19 INPATIENTS OR SUSPECTED CASES	COVID-19 TRANSPLANT INPATIENTS **12 beds**

2nd Floor:

Dialysis	COVID-negative nephrology ward