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Review Article

Kidney Disease Management during the COVID-19 Pandemic

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Abstract

The aim of the study was to summarize the kidney disease management–related literature during the unprecedented COVID-19 pandemic to attract clinicians' attention to strengthen kidney disease management. The patients were divided into six groups according to non-dialysis or dialysis, diagnosis with COVID-19 or without COVID-19. Kidney transplant patients were also included in the study. The agents commonly administrated by kidney disease patients such as corticosteroids, immunosuppressants, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker, chloroquine/hydroxychloroquine were also analyzed for their weaknesses and strengths during the COVID-19 pandemic. In addition, the risk and challenges that these patients faced were summarized and recommendations were given for clinicians and patients with kidney diseases to better manage kidney disease during the COVID-19.

***Keywords**: Kidney Disease; Management; COVID-19; Pandemic*

Introduction

The worldwide Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a global health emergency. The infection source of COVID-19 includes not only patients with clinical symptoms but also patients with asymptomatic pneumonia. The possible transmission modes of COVID-19 containing respiratory droplets, contact and fomites, nosocomial transmission, aerosol and fecal oral transmission, are highly probable [1]. The SARS-CoV-2 enters the host cells by binding to the angiotensin converting enzyme 2 (ACE2) receptor [2]. It was reported that ACE2 was highly expressed at the brush border of proximal tubular cells and podocytes [3]. Hematoxylin-eosin staining of renal tissues from six COVID-19 patients also showed severe acute tubular necrosis and lymphocyte infiltration [4]. Immunohistochemistry results indicated that SARS-CoV-2 nucleocapsid protein antigen was deposited in kidney tubules. Transmission electronic microscope also demonstrated that viruses-like particles were visible in the kidney tissues [4]. Previous studies showed that kidney disease was one of the most prevalent underlying diseases among hospitalized COVID-19 patients, and the prevalence was 0.83% [5]. The mechanism of kidney injury induced by COVID-19 may be related to direct virus attack, down-regulation of ACE2 expression, cytokine storm and immune injury. During the COVID-19 pandemic, traffic lockdown affects kidney disease management. However, the exact molecular mechanism needs to be further studied. Patients with kidney dysfunction had a worse clinical prognosis when infected with SARS-CoV-2 [6].

Purpose of the Study

The purpose of this study is to warn that we should not neglect kidney diseases while combating against COVID-19 and supply specific recommendations for patients with kidney diseases during the COVID-19 pandemic.

Kidney diseases and COVID-19

Non-dialysis dependent CKD (NDD-CKD) patients without COVID-19

NDD-CKD patients without COVID-19 are usually in an immunocompromised state due to long-term malnutrition, chronic inflammation, and oral corticosteroids or immunosuppressants. Moreover, NDD-CKD patients need regular examinations to warrant the effects of the treatment and adjust the therapeutic plans according to the test results. However, the city lockdown brings about tragedy for these NDD-CKD patients. Corticosteroids or immunosuppressants cannot be regulated for a long-term, resulting in a variety of secondary side effects and increasing the risk of SARS-CoV-2 infection [7]. These NDD-CKD patients have to discontinue therapies due to a lack of medications and possibly progress to end stage renal disease (ESRD). Therefore, online medical consultation is strongly recommended to reduce unnecessary hospital visits for patients and caregivers during the COVID-19 pandemic [8]. In addition, specific drug-supply chains (such as corticosteroids, immunosuppressants, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker, erythropoietin and iron supplement) should be established to guarantee the basic agents supply.

Dialysis dependent CKD (DD-CKD) patients without COVID-19

Maintenance hemodialysis (MHD) CKD (MHD-CKD) patients without COVID-19 confront with more difficulties during the COVID-19 pandemic. The traffic control during the COVID-19 pandemic is likely to block medical treatment for MHD-CKD patients. A number of hospitals have been designated as treating COVID-19 patients only, thereby the MHD-CKD patients probably cannot find hospitals that accept them to proceed with MHD. It is risky for HD-CKD patients if they cannot receive timely HD treatment. In addition, it is very difficult for MHD-CKD patients to access hospitals to examine and cope with kinds of ESRD-related complications. The MHD-CKD patients were suggested to wear personal protective equipments, keep hand hygiene, and measure body temperature regularly.

Although peritoneal dialysis (PD) CKD (PD-CKD) can be performed at home, PD-CKD patient still need extra attention. Unless doctor's guidance, PD-CKD patients are not able to estimate the adequacy of PD through examination and deal with kinds of complications such as peritonitis and heart failure. In addition, peritoneal dialysis solution and iodide-containing cap cannot be supplied because of traffic restriction. Erythropoietin cannot be injected regularly in hospital. During the course of PD, the patients and caregivers are required to wear medical masks and hats and must ensure the cleanness of the environment of PD. The room of the PD should be regularly ventilated and disinfected with ultraviolet rays. The instruments of PD need to be wiped with alcohol. If available, a remote management system should be implemented to provide timely feedback and improve treatment compliance and efficacy of PD [8].

NDD-CKD patients with COVID-19

So far, there is no effective targeted therapy for NDD-CKD patients with COVID-19. In addition, although 45% of patients with COVID-19 received corticosteroids treatment, the benefits of hormone therapy are still unclear [9]. The efficacy of chloroquine has been verified in a small clinical trial [10], but the side effects based on the drug have not been verified in large-scale clinical studies. It is controversial for NDD-CKD patients with COVID-19 whether or not they should continue their previous remedies.

Corticosteroids

Corticosteroids are commonly employed in the treatment of different kidney diseases. The expert consensus statement from China conducted exhaustive principles that should be followed when using corticosteroids [11]. Patients with nephrotic syndrome who regu-

larly take corticosteroids before infected COVID-19 can continue corticosteroids treatment after nephrologist consultation according to the expert consensus statement. However, the World Health Organization (WHO) stresses that corticosteroids should not be used systematically and routinely in the treatment of 2019-nCoV infection [12]. In line with WHO guidance, Clark Russell and colleagues concluded that corticosteroids should not be applied for the treatment of 2019-nCoV-induced lung injury because corticosteroids retard lung inflammation but also inhibit immune responses and virus clearance [13]. However, a panel of front-line expert physicians from China recommended using short courses of low-to-moderate dose corticosteroids cautiously for critically ill patients with COVID-19 [14]. A retrospective cohort study also showed that corticosteroids were beneficial for the survival curves of COVID-19 patients with risk of acute respiratory distress syndrome [15].

COVID-19 patients who take corticosteroids for a long time have differed clinical features. A 47-year-old woman with systemic lupus erythematosus (SLE) using long-term glucocorticoids did not present any symptoms within the 14-day quarantine period but was confirmed with COVID-19 to day 40, which suggests that the long-term use of glucocorticoids might lead to asymptomatic infections, a long incubation period and extra transmission of COVID-19 [16].

Immunosuppressants

Calcineurin inhibitors (CNIs) are wildly applied to a variety of kidney diseases including renal transplantation recipients.

Cyclophilin A is a receptor for cyclosporin A (CsA). Cyclophilin A is essential for the replication of various coronaviruses such as SARS-CoV, CoV-229E, CoV-NL63, and FCoV [17]. Alisporivir, a non-immunosuppressive analogue of cyclosporin A, which decreased SARS-CoV-2 RNA production in a dose-dependent manner in VeroE6 cell line [18]. Meanwhile, CsA have prominent inhibitory effects on various coronaviruses [19]. *In vitro* experiments also demonstrated that FK506 (Tacrolimus) strongly inhibited the replication of human coronaviruses SARS-CoV, HCoV-NL63, and HCoV-229E at low, non-cytotoxic concentrations [20]. These findings may support CNIs' continuous use as the preferred maintenance immunosuppressants in transplant patients with COVID-19 [21]. The availability of other immunosuppressants such as mycophenolate mofetil, cyclophosphamide in COVID-19 is unclear.

ACEI/ARB

ACEI/ARB is routinely applied to control blood pressure and reduce proteinuria in kidney diseases. There are controversies regarding ACEI/ARB owning to two competing hypothetical mechanisms by which ACEI or ARB might be harmful or protective during the COVID-19 pandemic [22].

COVID-19 patients with hypertension who took ACEI or ARB had a lower rate of severe disease and a lower level of IL-6 expression in peripheral blood [23]. Additionally, ACEI or ARB therapy reduced the peak viral load compared to other antihypertensive drugs [23]. In keeping with the above results, treatment with ACEI was associated with a decreased rate of death or transfer to a critical care unit within 7 days in patients with COVID-19 [24]. Meanwhile, a meta-analysis demonstrated that elderly COVID-19 patients with hypertension taking ARB could mitigate disease activity [25]. In view of this, it is concluded that patients being treated with ACEIs and ARBs should continue their treatment for approved indications [26].

Chloroquine/hydroxychloroquine

Chloroquine is well known for its antimalarial effects. Hydroxychloroquine is one of the cornerstone regimens for the treatment of SLE and lupus nephritis. Chloroquine and hydroxychloroquine belong to the same molecular family. Currently, chloroquine has been repurposed in the treatment of various viruses including members of the flaviviruses, retroviruses, and coronaviruses [27]. The chloroquine possesses antiviral effects by interfering with viral particles binding to their cellular cell surface receptors, pH-dependent endosome-mediated viral entry of enveloped viruses, post-translational modification of viral, and regulation of pro-inflammatory cytokines [28].

DD-CKD with COVID-19

HD-CKD patients have to be exposed to hospital settings 2 - 3 times a week, which predisposes them to a significant risk for experiencing SARS-CoV-2 infection.

For DD-CKD patients diagnosed with COVID-19, HD or PD must be performed in different designated departments or hospitals according to disease severity. The dialysis center should rearrange the hemodialysis rooms and intend partially for patients with SARS-CoV-2 infection and partially for patients who are negative for SARS-CoV-2 [29] and clinical suspicion cases. The room intended for suspected cases should be arranged in case of urgency for dialysis treatment. If the clinical suspicion of COVID-19 emerged, the patient should be sent to perform specific testing [29]. PD-CKD patients with COVID-19 should be prudent to avoid SARS-CoV-2-related peritonitis. If SARS-CoV-2-related peritonitis occurred or progressed to critical illness, PD should be replaced by HD to improve clinical outcomes. The Chinese expert panel had advocated consensus recommendations for the care of children receiving maintenance dialysis in COVID-19 pandemic [8].

Kidney transplant patients without COVID-19

In the COVID-19 outbreak, the traffic restriction caused by the regional lockdown is probably affect the examination of renal transplant patients, which may delay the adjustment of treatment plans and the occurrence of transplant rejection, or even recurrent renal failure. Hence, telemedicine was strongly recommended for them to minimize unintended exposure to clinic staffs and other patients [30]. All kidney transplant patients should be instructed to practice social distancing, maintain good hand hygiene, and wear personal protective equipment during the COVID-19 pandemic [30].

Kidney transplant patients with COVID-19

Because of long-term use of immunosuppressive agents, transplant patients may have unspecified viral clinical presentation [31] or delayed presentation of serious infections [30]. Consequently, a more proactive approach in the diagnostic evaluation and monitoring of renal transplant patients and a lower threshold for hospitalization are appropriate [30].

A kidney transplant patient with COVID-19 receiving tacrolimus (1 mg twice a day, orally), mycophenolate mofetil (0.5g twice a day, orally), and prednisone (5 mg daily, orally) had prolonged viral shedding than the general population with COVID-19 [32]. In this case, immunosuppressants were discontinued, and systemic methylprednisolone (40mg daily, intravenously) was given to reduce inflammation [32].

Because of their systemic immunosuppressive state caused by anti-rejection drugs, kidney transplant patients with COVID-19 might have a poorer prognosis. Therefore, how to adjust the anti-rejection drugs may be a key issue in the treatment. It has been reported that a kidney transplant patient with COVID-19 recovered without reducing the immunosuppression therapy [33]. On one hand, the immunosuppression state can prevent multiple organ dysfunction caused by excessive inflammation and cytokine release [33]. On the other hand, CsA, as a commonly used immunosuppressant, can inhibit the replication of a variety of coronaviruses [33]. Taken together, immunosuppression regimen adjustment need be considered for kinds of factors such as time since transplantation, baseline graft function, prior history of rejection, age, and presence of donor-specific antibodies and the balance between controlling infection and maintaining graft function [30].

COVID-19 patients with concurrent renal involvement

Patients with COVID-19 may suffer from kidney involvement even if they have no kidney diseases in the past, which may be caused by direct virus damage, cytokine storm syndrome, other factors such as fluid loss, drug toxicity, and previous underlying diseases.

The renal injury of COVID-19 patients is associated with in-hospital death [34], thereby it is important to improve the renal function in time for the treatment of COVID-19 patients. For patients infected with COVID-19 who had abnormal urinalysis, 24-hour urine protein quantification should be screened to identify kidney involvement. If necessary, consultation with nephrologists is required. In the process of treatment, we should avoid applying nephrotoxicity agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be applied carefully in case of fever. In case of gastrointestinal symptoms such as nausea, vomiting, diarrhea, and shock, we need to be alert to the risk of acute renal injury (AKI) because of hypoperfusion. In the case of myalgia, we need to be alert to myolysis. We should pay special attention to AKI, which is an independent risk factor of death, and the risk of rapidly progressive glomerulonephritis. If necessary, renal biopsy is needed to make an accurate diagnosis. Plasma purification, absorption, perfusion, blood/plasma filtration, and other blood purification techniques should be performed for critically ill patients with high inflammatory response [35].

Conclusion

Kidney is involved in COVID-19. Clinicians need to pay attention to the potential risks leading to kidney injury and take measures to avoid kidney injury. For the kidney disease patients, it is necessary to effectively manage them according to their risks.

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Declaration of Competing Interest

All authors state that there is no conflict of interest.

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Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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