



Recommendation and Consensus

Management recommendations for patients with chronic kidney disease during the novel coronavirus disease 2019 (COVID-19) epidemic

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Abstract

COVID-19 has become a pandemic and it has already spread to at least 171 countries/regions. Chronic kidney disease (CKD) is a global public health problem with a total of approximately 850 million patients with CKD worldwide and 119.5 million in China. Severe COVID-19 infection may damage the kidney and cause acute tubular necrosis, leading to proteinuria, hematuria and elevated serum creatinine. Since the SARS-CoV-2 enters the cells by binding to the angiotensin-converting enzyme 2 receptor, some doctors question its ability to increase the risk and severity of developing COVID-19. Neither clinical data nor basic scientific evidence supports this assumption. Therefore, patients who take angiotensin-converting enzyme inhibitor or angiotensin receptor blocker are not advised to change their therapy. Patients with CKD are generally the elderly population suffering from multiple comorbidities. Moreover, some patients with CKD might need to take glucocorticoids and immunosuppressants. Dialysis patients are recurrently exposed to a possible contaminated environment because their routine treatment usually requires three dialysis sessions per week. Considering all the above reasons, patients with CKD are more vulnerable to COVID-19 than the general population. The development of COVID-19 may worsen the impaired kidney function and further lead to rapid deterioration of kidney function and even death. Strict comprehensive protocols should be followed to prevent the spread of COVID-19 among patients with CKD. In this review, we provide some practical management recommendations for health care providers, patients with CKD, dialysis patients and dialysis facilities.

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Since the outbreak of the coronavirus disease 2019 (COVID-19) in China,^{1,2} it has spread to at least 171 countries/regions.³ As of March 22, 2020, there were 305,234 confirmed cases and 13,004 deaths all over the world.³ The disease of COVID-19 was earlier called the “2019 novel coronavirus pneumonia” On February 12, 2020, the World Health Organization (WHO) officially named it as “COVID-19.” The virus responsible for

COVID-19 was announced as “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) by the International Virus Classification Commission.⁴ The WHO declared COVID-19 as a pandemic on March 11, 2020. The coronavirus family was responsible for two previous pandemic outbreaks of infectious respiratory diseases: severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). In comparison with SARS and MERS, COVID-19 is more contagious and has a lower fatality rate.⁵

The morbidity and fatality of COVID-19 are much higher in members of the senior population who manifest multiple comorbidities.⁶ Patients with chronic kidney disease (CKD) usually have several comorbidities, such as hypertension, diabetes, and cardiovascular diseases. CKD is a global public health problem with a total of approximately 850 million patients with CKD worldwide.⁷ In China, the incidence of CKD is 10.8% and estimates indicate that 119.5 million Chinese adults have CKD.⁸ Patients with CKD are highly susceptible to COVID-19. In addition, patients on hemodialysis need to visit the dialysis center regularly three times every week. Therefore, the dialysis center becomes a potential vector responsible for spreading this pandemic. In previous epidemics or catastrophic situations, the fatality rate was much higher in patients on dialysis than that in the general population.⁵ This review aimed to provide management recommendations for patients with CKD during the COVID-19 epidemic period.

Acute kidney injury (AKI) in patients with COVID-19

There is no evidence that COVID-19 infection affects the kidneys in patients with mild-to-moderate illness. However, kidney abnormalities are observed in 20%–63% of the severe patients who require hospitalization. These are manifested as the presence of protein and red blood cells in the urine; a small proportion had elevated levels of plasma creatinine (19%) and urea nitrogen (27%).⁹

In a case series of 710 patients with COVID-19, the incidence of proteinuria and hematuria on admission was reported to be 44% and 22%, respectively.¹⁰ Some patients displayed elevated serum creatinine levels and edema of the renal parenchyma under the computed tomography (CT) scan. Pathological findings from six autopsy specimens revealed severe acute tubular necrosis (ATN) on inspection under a light microscope. Further immunohistochemical examination revealed the presence of the SARS-CoV-2 nucleocapsid protein in the kidneys, suggesting direct tubular injury from

the virus.¹¹ It is difficult to evaluate the precise incidence of AKI in patients with COVID-19. The incidence of AKI in published reports is 2%–5%. However, most of them were from severely ill hospitalized patients. Therefore, the risk in patients with mild illness might be much lower. The incidence of AKI in SARS patients with normal kidney function (without underlying CKD) is reported to be 6.7%; this was mostly due to ATN and occasional rhabdomyolysis.¹² Moreover, it may even lead to a multiple organ dysfunction syndrome (MODS). The SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase (DPP4). These enzymes are highly expressed in the kidneys; they might serve as binding sites for the virus and cause kidney injury. Although the mortality rate is much higher in SARS patients with AKI than those without AKI (92% vs 8%),¹² it remains unknown whether AKI leads to increased mortality in patients with COVID-19.^{6,9}

COVID-19, hypertension, angiotensin-converting enzyme inhibitor (ACEI), and angiotensin receptor blocker (ARB)

In literature, approximately 15%–30% of patients with COVID-19 manifest hypertension.¹³ Hypertension is assumed to be an independent risk factor for developing COVID-19 and worsening the disease severity. To date, we have no evidence to support the relationship between hypertension and COVID-19. Hypertension increases with age. The COVID-19 disease is more severe and displays worse outcomes in the elderly population.^{14,15} After adjustment of age, the association between COVID-19 and hypertension was non-existent.¹⁶ Many coronaviruses, including the SARS-CoV-2, enter the cells by binding to the ACE2 receptor. Therefore, the risk and severity of COVID-19 might vary with the level of ACE2 receptor.¹³ The ACEI and ARB are widely used as medications in the treatment of hypertension. As the application of ACEI and ARB leads to an increase in the concentration of ACE2, some doctors question its ability to increase the risk and severity of developing COVID-19 as well.¹³ Neither clinical data nor basic scientific evidence supports this assumption. Therefore, patients who take ACEI or ARB are not advised to change their therapy.¹³

Patients with CKD are vulnerable to COVID-19

Firstly, SARS-CoV-2 enters the human body through the human ACE2 and human DPP4 (also known as CD26) as the main receptors.^{17,18} ACE2 and DPP4 are

highly expressed in the kidney, especially in the renal tubules. If patients with CKD get infected with SARS-CoV-2, their renal tubules are likely to be attacked first. Secondly, patients with CKD are generally the elderly population suffering from multiple comorbidities. They usually have imbalanced ratios of CD4⁺/CD8⁺ T cells and decreased activity of natural killer cells. Moreover, some patients with CKD (for whom glomerular disease is the reason for developing CKD), might need to take glucocorticoids and immunosuppressants. This may further lead to impairment of their immune system and create increased susceptibility to COVID-19. Thirdly, there are several small arteries and capillaries in the kidney that may be damaged by the SARS-CoV-2. Further, the entire volume of blood passes through the kidneys several times a day. Hence, the virus and the inflammatory cytokines in the blood flow can damage the kidneys. Lastly, as a severe subgroup of patients with CKD, dialysis patients constitute a more susceptible population. Dialysis patients are recurrently exposed to a possible contaminated environment because their routine treatment usually requires three dialysis sessions per week.⁵ Considering all the above reasons, patients with CKD are more vulnerable to COVID-19 than the general population. The development of COVID-19 may worsen the impaired kidney function and further lead to rapid deterioration of kidney function and even death.

Recommendations for health care providers^{5,18,19}

1. Full protection, including waterproof isolation clothing, hair caps, goggles, gloves, and medical masks (surgical mask or the N95 mask) should be undertaken by all the personnel involved in direct patient care. Hand hygiene should be strictly implemented.
2. Training on the updated clinical knowledge of the COVID-19 epidemic, epidemic prevention tools, and guidelines from organizations with authority should be provided to all personnel, including the dialysis physicians, nursing staff, and technologists.
3. Information on travel, occupation, contacts, and cluster history of each staff should be collected and updated regularly.
4. Group activities, including group studies and case discussions, should be avoided.
5. The staff members should have meals at different times to avoid dining together. Talking during meals should be minimized to reduce the spread of droplets.

6. The symptoms of the staff should be self-monitored and their leader informed in case of development of suspicious symptoms by them or their family members.

General recommendations for patients with CKD^{5,18,19}

1. Hands should be washed frequently with soap and flowing water or using an alcohol-based hand sanitizer. Touching of eyes, nose, and mouth with unwashed hands should be avoided. People should stay at home and maintain distance from others. Coughing or sneezing into a tissue or a flexed elbow should be practiced. Objects and surfaces that are frequently touched should be cleaned regularly.
2. Touching of surfaces used in public places should be avoided. A hand towel or tissue should be used when touching doorknobs, light switches, etc. Close contact with sick people and greeting people with a handshake, hug, or a kiss should be avoided. Shoes should be removed outside the house before entering.
3. Medicines should be continued by all patients in prescribed doses and under strict compliance with doctor's instructions unless advised otherwise by their treating doctors. These include the ACE inhibitors and medications for the treatment of hypertension, diabetes, anemia, and urinary protein. All drugs should be continued, especially glucocorticoids or immunosuppressants. Injection therapy, such as cyclophosphamide injection therapy, can be replaced with oral cyclophosphamide or other immunosuppressants under the guidance of a doctor. Subcutaneous injection of erythropoietin can also be replaced by oral drugs. The doctor should be contacted if feeling sick.
4. Unnecessary hospital visits should be avoided because patients with CKD are susceptible to COVID-19 and hospitals are high-risk places with some potentially-infected patients. The maximum possible drugs must be procured in every hospital. The necessary drugs must be procured from a nearby pharmacy during a visit to the community hospital for some routine examination. A face mask must be worn during illness and around people or while visiting a health facility. Attending doctors must be contacted using online consultation tools, such as

professional medical websites, e-mail, and social media (Facebook, WeChat, etc).

5. **Diet Management:** Extra attention should be paid to food safety and food hygiene issues. Food intake should be diversified. The daily meals should include cereals, vegetables and fruits, livestock, poultry, fish, eggs, milk, soy-beans, etc. The protein intake should be reasonably guaranteed. The daily protein intake of non-dialyzed CKD patients should preferably range from 0.6 to 0.8 g/kg/d; a high-quality protein intake comprising fish, shrimp, lean meat, eggs, beans, etc. should account for 60%–70% of the total food constituents. The intake of salt, potassium, phosphorus, and purines should be strictly limited. Moderate amounts of milk and water should be consumed and carbonated drinks, coffee, and alcohol should be avoided.
6. **Psychological management:** In the crisis of the COVID-19 outbreak, patients with CKD are more likely to have negative emotions. Excessive and persistent psychological reactions have serious consequences and may lead to irrational behavior and severe physical conditions. Common psychological problems include nervousness, anxiety, depression, sleep disorders, obsessive-compulsive symptoms, physical symptoms, and stress-related physical diseases. A correct cognition towards this crisis should be established. A healthy regular lifestyle with sufficient work and regular rest should be established. Communication with relatives and friends through social media should be encouraged. An overload of information should be avoided and a happy mood should be maintained. Online psychological counseling should be resorted to, if necessary.

Recommendations for dialysis patients and dialysis facilities^{5,18,19}

1. Entrance control, identification, and shunting of people at risk of infection, body temperature measurement, and hand washing should be instituted. All patients should have their temperature monitored on arrival for dialysis. Patients and their accompanying persons should be given hands-free hand sanitizer while entering the dialysis room.

2. Meals should be avoided by patients during dialysis; convenience food such as candy can be taken to prevent hypoglycemia.
3. The dialysis units should be intimated before the arrival of patients with fever or respiratory symptoms. Such patients should be assessed in a room or area separate from the dialysis area and should be screened for COVID-19 infection. Moreover, they should be administered regular dialysis in the last shift of the day until COVID-19 infection is excluded.
4. Public transport should be avoided. The pick-up and drop-off points should not be shared with other dialysis patients. Entering and exiting with other patients at the same time should be avoided.
5. Patients should not be in close proximity, face masks should be worn throughout the dialysis process. The treatment and waiting areas should have good air-conditioning and ventilation to remove droplet particles from the air.
6. Equipment and environment coming in contact with patients or potentially contaminated materials should be disinfected according to standard protocols.

In summary, severe COVID-19 infection may damage the kidney and cause ATN, leading to proteinuria, hematuria, and elevated serum creatinine. Neither clinical data nor basic scientific evidence supports the idea that ACEI or ARB can increase the risk and severity of developing COVID-19. Therefore, patients who receive ACEI or ARB should not change their therapy unless advised by their physician. Patients with CKD are highly susceptible to COVID-19. Strict comprehensive protocols should be followed to prevent the spread of COVID-19 among patients and healthcare providers.

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Conflict of interest

None.

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