The Novel Coronavirus 2019 epidemic and kidneys

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Novel Coronavirus disease (COVID-19) is a newly discovered contagious disease caused by severe acute respiratory syndrome (SARS)–coronavirus (CoV)-2 virus, primarily manifesting as an acute respiratory illness with interstitial and alveolar pneumonia, but it can affect multiple organs such as the kidney, heart, digestive tract, blood, and nervous system.[1] The rapidly spreading outbreak, which first emerged in Wuhan, Hubei Province, China, in December 2019, has since been declared a global pandemic. As of March 16, 2020, 167,511 cases of COVID-19 have been reported worldwide in 151 countries (and a cruise ship), with 6606 deaths.[2] In recent days, the number of cases has risen rapidly in South Korea, Japan, Europe, and the United States.

SARS-CoV-2 has been identified as a bat-origin CoV. The full-length genome sequence of the COVID-19 virus shows a close relationship with the bat SARS-like coronavirus strain BatCov RaTG13 belonging to the *Betacoronavirus* genus.[3]

Previous coronavirus infections, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-Co-V), have infected more than 10,000 people in the past 2 decades, with mortality rates of 10% and 37%, respectively.[4,5] COVID-19 is more contagious than these illnesses, spreads by human-to-human transmission via droplets, fecal, or direct contact, and has an incubation period estimated at 1 to 14 days (usually 3 to 7 days).

Infection has been reported in all ages, including children. The majority of infections are mild, presenting with a flu-like illness. The common clinical presentations of COVID-19 are fever (98%), cough (76%), and myalgia and fatigue (18% each),[6] with accompanying leucopenia (25%) and lymphopenia (63%). Symptoms of upper respiratory infection with rhinorrhea and productive cough are uncommon, except in children. About 16% to 20% cases have been classified as *severe* or *critical*. Of the 41 patients described by Huang *et al.*,[6] all had pneumonia with abnormalities on computerized tomographic examination of the chest (bilateral lobular and subsegmental areas of consolidation), and 32% required care from the intensive care unit. Higher plasma cytokine levels (interleukin [IL]-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-inducing protein-10, monocyte chemoattractant protein 1, macrophage inflammatory protein-1a, tumor necrosis factor α) were present in patients requiring intensive care unit admission. Limited reports suggest that severe complications are uncommon in children.[7]

Diagnosis

The diagnosis is mainly based on epidemiological factors (history of contact), clinical manifestations, and laboratory examination (hemogram, chest computed tomography, and virological examination).[8] Of note, there are recent cases without any travel history or apparent contact with infected individuals. Several COVID-19 nucleic acid detection assays have been developed, both in-house and commercial. They use fluorescence polymerase chain reaction and probe anchoring polymerization techniques. Gene sequencing has also been used. The World Health Organization has appointed referral laboratories in different countries.[9] A serological test has been developed and allowed detection of a cluster of cases in Singapore.[10] More sensitive and convenient detection methods continue to be developed.

Kidney involvement in COVID-19 infection

In previous reports of SARS and MERS-CoV infections, acute kidney injury (AKI) developed in 5% to 15% cases and carried a high (60%–90%) mortality rate. Early reports suggested a lower incidence (3%–9%) of AKI in those with COVID-19 infection.[1,11–13] Recent reports, however, have shown higher frequency of renal abnormalities. A study of 59 patients with COVID-19 found that 34% of patients developed massive albuminuria on the first day of admission, and 63% developed proteinuria during their stay in hospital.[14] Blood urea nitrogen was elevated in 27% overall and in

two-thirds of patients who died. Computed tomography scan of the kidneys showed reduced density, suggestive of inflammation and edema. Cheng *et al.*[13] recently reported that amongst 710 consecutive hospitalized patients with COVID-19, 44% had proteinuria and hematuria and 26.7% had hematuria on admission. The prevalence of elevated serum creatinine and blood urea nitrogen was 15.5% and 14.1%, respectively. AKI was an independent risk factor for patients' in-hospital mortality.[13,14]

Pathogenesis of kidney injury

The exact mechanism of kidney involvement is unclear: postulated mechanisms include sepsis leading to cytokine storm syndrome or direct cellular injury due to the virus. Angiotensin-converting enzyme and dipeptidyl peptidase-4, both expressed on renal tubular cells, were identified as binding partners for SARS-CoV and MERS-CoV, respectively.[15,16] Viral RNA has been identified in kidney tissue and urine in both infections.[17,18] Recently, Zhong's lab in Guangzhou successfully isolated SARS-CoV-2 from the urine sample of an infected patient, suggesting the kidney as the target of this novel coronavirus.[19]

Treatment

The current treatment of COVID-19 with AKI includes general and supportive management and kidney replacement therapy. There is no effective antiviral therapy available at present.

General management. All patients with confirmed COVID-19 need to be quarantined. An N95 fit-tested respirator and protective clothes and equipment are essential. Early admission to intensive care units in designated hospitals is recommended for severely ill patients.

Supportive care, namely bed rest, nutritional and fluid support, and maintenance of blood pressure and oxygenation are important measures, as for all critically ill patients. Other measures include prevention and treatment of complications by providing organ support, maintaining hemodynamic stability, and preventing secondary infection.

Antiviral therapy. There is no specific effective antiviral drug for COVID-19 at present. The guidelines of the Chinese National Health Commission recommend aerosolized inhalation of interferon α and lopinavir/ritonavir. The specific therapeutic value and safety of lopinavir/ritonavir in patients with COVID-19 are under investigation (ChiCTR2000029308).[20] Successful treatment with remdesivir has been reported in a patient with COVID-19; a clinical trial on the efficacy of remdesivir in patients with COVID-19 is currently underway in China (NCT0425266; NCT04257656) and is expected to be completed in April 2020. Chloroquine phosphate has been shown to have some efficacy against COVID-19–associated pneumonia in multicenter clinical trials conducted in China.[21]

Extracorporeal treatments. Continuous renal replacement therapy (CRRT) has been successfully applied in the treatment of SARS, MERS, and sepsis.[22,23] High-volume hemofiltration in a dose of 6 l/h removed inflammatory cytokines (IL-6) and improved the Sequential Organ Failure Assessment scores at day 7 in patients with sepsis.[24] Therefore, CRRT may play a role in patients with COVID-19 and sepsis syndrome. The potential role of extracorporeal therapy techniques needs to be evaluated, however.

Glucocorticoids. In a retrospective study of patients with SARS-CoV and sepsis, steroids, at a mean daily dose of 105.3 $\pm$ 86.1 mg in 147 of 249 noncritical patients (59.0%), reduced mortality rate and shortened duration of hospitalization, whereas 121 of 152 critical patients (79.6%) received corticosteroids at a mean daily dose of 133.5 $\pm$ 102.3 mg, and 25 died.[25] A subsequent retrospective, observational study of 309 patients with MERS showed that those who received high-dose steroids were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy (RRT).[26] In a meta-analysis of corticosteroid use in patients with SARS, 4 studies provided conclusive evidence of harm (psychosis, diabetes, avascular necrosis, and delayed viral clearance).[27] Therefore, the use of steroids is controversial and not recommended by the World Health Organization because of potential inhibition of viral clearance and prolongation of the duration of viremia.[28]

Convalescent plasma. Preliminary clinical studies in China have shown that early application of convalescent plasma in patients with COVID-19 could accelerate clinical recovery.[6] Currently 2 trials, an open-label, non-randomized clinical trial (NCT04264858) and a multicenter, randomized, and parallel-controlled trial (ChiCTR2000029757) on the efficacy of convalescent plasma in patients with COVID-19, are underway in China.

Monoclonal antibody. Monoclonal antibody directed against the Ras-binding domain of the S protein of MERS-CoV has been found to have neutralizing activities in plaque assays

in vitro.[29] A monoclonal antibody against COVID-19 has not yet been developed. Tocilizumab, a monoclonal antibody against the IL-6 receptor, has achieved encouraging preliminary clinical results. The safety and efficacy of tocilizumab in COVID-19 infection are undergoing evaluation by a multicenter randomized controlled trial (ChiCTR2000029765).

COVID-19 in patients with kidney disease

Pregnant women, newborns, the elderly, and patients with comorbidities like diabetes mellitus, hypertension, and cardiovascular disease are susceptible to COVID-19 infection and are likely to have more severe illness often requiring care from an intensive care unit. The impact of COVID-19 on chronic kidney disease has not been reported.[30]

COVID-19 infection presents a special threat to patients on dialysis. There are 7184 patients on hemodialysis (HD) in 61 treatment centers in Wuhan City. At a single HD center in Renmin Hospital, Wuhan University, 37 out of 230 patients on HD and 4 of 33 staff members developed COVID-19 infection between January 14 and February 17, 2020.[30] A total of 7 patients on HD died, of whom 6 had COVID-19 infection. However, the deaths were deemed to be due to cardiovascular causes and not directly to the COVID-19 infection. Patients on HD with COVID-19 had less lymphopenia, lower serum levels of inflammatory cytokines, and milder clinical disease than other patients with COVID-19 infection.

Management of patients on dialysis

COVID-19 infection presents particular challenges for patients on dialysis, in particular, those in in-center HD. Patients with uremia are particularly vulnerable to infection and may exhibit greater variations in clinical symptoms and infectivity. In-center HD significantly increases the risk of transmission of infection, including to medical staff and facility workers, patients themselves, family members, and all others.

The Chinese Society of Nephrology[31] and the Taiwan Society of Nephrology[32] have recently developed guidelines for dialysis units during the COVID-19 outbreak. A summary of these guidelines is provided below.

1. A working team consisting of dialysis physicians, nursing staff, and technologists should receive training in updated clinical knowledge of epidemic COVID-19, notification of infection at risk, epidemic prevention tools, and guidelines from the government, academic society, and hospital authority. The list of staff should be recorded and retained by dialysis hospitals.
2. Information on travel, occupation, contacts, and cluster (TOCC) history of each medical staff, dialysis patient, their family members, residents of the same institution, and colleagues at work should be collected and updated regularly.
3. Latest care recommendations and epidemic information should be updated and delivered to all medical care personnel as needed. Training can be done peer-to-peer or online.
4. Group activities, including group rounds, group studies, and case discussions, should be minimized.
5. It is recommended that staff members have meals at different times to avoid dining together. Goggles, masks, and hats should be removed before meals, and hands washed with flowing water. Talking during meals should be minimized to reduce the spread of droplets.
6. Staff should self-monitor their symptoms and should inform the team leader in case they or their family members develop symptom(s) suggestive of COVID-19 infection.
7. Entrance control, identification and shunting of people at risk of infection, body temperature measurement, hand washing, wearing of proper (surgical or N95) masks throughout the process, machine disinfection, environmental cleanliness, good air conditioning, and ventilation conditions should be instituted.
8. Patients and accompanying persons should be given motion-activated hand sanitizer while entering the dialysis room. Patients should wear medical masks and avoid meals during dialysis. They can bring convenience food such as candy to prevent hypoglycemia.
9. Patients with suspected or confirmed COVID-19 infection should be admitted to a negative-pressure isolation ward of specified hospitals. If the capacity of the isolation facility is overloaded, the *Fixed Dialysis Care Model* detailed below is recommended for dialysis patients under the 14-day period of quarantine for possible contact with COVID-19.
   a. Place of dialysis treatment: patients should continue HD at the original HD center and not change to another center.

b. Dialysis shift and personnel: do not change dialysis shifts and caregiver staff to avoid cross-contamination and infection. Minimize the relevant contacts.
c. Patients who need vascular access surgery should be screened for novel coronavirus before the surgery. Operations on patients with confirmed or suspected novel coronavirus infection should be carried out in a designated room with necessary protection for medical staff.
d. Transportation: public transport should not be used. Patients should arrange personal transportation and take fixed transportation routes. Transport personnel and escorts should wear surgical-grade or N95 masks throughout.
e. All patients who have fever should be screened for novel coronavirus infection and should be given dialysis in the last shift of the day until infection is excluded.
f. Pass route for entering hospital and dialysis unit: 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. The route, mode, and time of transport of dialysis personnel should be fixed.
g. Precautions in dialysis unit: patients should not be in close proximity; treatment and waiting areas should have good air conditioning and ventilation to remove droplet particles from the air.
h. Designated care personnel: all personnel involved in direct patient care should undertake full protection, including long-sleeved, waterproof isolation clothing; hair caps; goggles; gloves; and medical masks (surgical mask grade or above). Hand hygiene should be strictly implemented.
i. Dialysis machine: equipment that may come into contact with patients or potentially contaminated material should be disinfected according to standard protocols.

10. If a newly confirmed or highly suspected case of novel coronavirus infection in dialysis centers is identified, disinfection should be carried out immediately. Areas in close contact with these patients should not be used for other patients until cleared.
11. The medical waste from confirmed or suspected patients with novel coronavirus infection should be considered as infectious medical waste and disposed accordingly.

Operational strategies for family member and caregivers

(i) All family members living with patients on dialysis must follow all the precautions and regulations given to patients to prevent person-to-person and within-family transmission of COVID-19, which include body temperature measurement, good personal hygiene, handwashing, and prompt reporting of potentially sick people.
(ii) Patients on dialysis who have a family member or caregiver subject to *basic quarantine* can have dialysis as usual in accordance during the 14-day period.
(iii) Once the family members or caregiver of a patient on dialysis have been converted to a confirmed case, the patient's identity should be upgraded and treated in accordance with the above-mentioned conditions.

In summary, COVID-19, a pandemic caused by a novel coronavirus, is a major global human threat. Kidney involvement seems to be frequent in this infection, and AKI is an independent predictor of mortality. The impact of this infection in those with chronic kidney disease has not been studied. Management of patients on dialysis who have been suspected to have been in contact with COVID-19 should be carried out according to strict protocols to minimize risk to other patients and healthcare personnel taking care of these patients.

DISCLOSURE

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REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. https://doi.org/10.1001/jama.2020.1585. Accessed March 2, 2020.
2. World Health Organization. Coronavirus disease (COVID-2019) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed March 16, 2020.
3. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Available at: https://www.who.int/docs/default-

source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed March 2, 2020.
4. World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Available at: https://www.who.int/csr/sars/country/table2004_04_21/en/. Accessed January 27, 2020.
5. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). November 2019. Available at: http://www.who.int/emergencies/mers-cov/en/. Accessed February 27, 2020.
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395:497–506.
7. Center for Disease Control and Prevention. Frequently asked questions and answers: Coronavirus Disease-2019 (COVID-19) and children. Available at: https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/children-faq.html. Accessed March 2, 2020.
8. Ling L, Taisheng L. The National Health Commission of PRC Guideline for diagnosis and treatment of novel coronavirus disease (version 6). *Natl Med J China*. 2020;100:E001.
9. World Health Organization. Specimen referral for 2019nCoV - operational details of referral laboratories. Available at: https://www.who.int/docs/default-source/coronaviruse/who-appointed-2019-ncov-referral-laboratories-7-february-2020.pdf?sfvrsn=c3fa3ec3_4. Accessed March 2, 2020.
10. Normile D. Singapore claims first use of antibody test to track coronavirus infections. Available at: https://www.sciencemag.org/news/2020/02/singapore-claims-first-use-antibody-test-track-coronavirus-infections. Accessed March 2, 2020.
11. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507–513.
12. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China [e-pub ahead of print]. *N Engl J Med*. https://doi.org/10.1056/NEJMoa2002032. Accessed March 2, 2020.
13. Cheng Y, Luo R, Wang K, et al. Kidney impairment is associated with in-hospital death of COVID-19 patients [e-pub ahead of print]. medRxiv 2020.02.18.20023242. https://doi.org/10.1101/2020.02.18.20023242. Accessed March 2, 2020.
14. Li Z, Wu M, Guo J, et al. Caution on kidney dysfunctions of 2019-nCoV patients. medRxiv 2020.02.08.20021212. Accessed March 2, 2020.
15. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426:450–454.
16. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature*. 2013;495:251–254.
17. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*. 2003;361:1767–1772.
18. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol*. 2004;203:622–630.
19. The team of Zhong Nanshan responded that the isolation of SARS-CoV-2 from urine remind us to pay more attention to the cleaning of individuals and families. *Guangzhou Daily*. Published February 22, 2020.
20. Expert Team of Chinese Society of Nephrology. Expert consensus on diagnosis and treatment of 2019 novel coronavirus (2019 - nCoV) infection with acute kidney injury. *Chin J Nephrol*. 2020;3. https://doi.org/10.3760/cma.j.cn441217-20200222-00035.
21. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14:72–73.
22. Chu KH, Tsang WK, Tang CS, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int*. 2005;67:698–705.
23. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med*. 2014;160:389–397.
24. Ghani RA, Zainudin S, Ctkong N, et al. Serum IL-6 and IL-1-ra with sequential organ failure assessment scores in septic patients receiving high-volume haemofiltration and continuous venovenous haemofiltration. *Nephrology (Carlton)*. 2006;11:386–393.
25. Chen RC, Tang XP, Tan SY, et al. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. *Chest*. 2006;129:1441–1452.
26. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197:757–767.
27. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3:e343.
28. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395:473–475.
29. Park BK, Maharjan S, Lee SI, et al. Generation and characterization of a monoclonal antibody against MERS-CoV targeting the spike protein using a synthetic peptide epitope-CpG-DNA-liposome complex. *BMB Rep*. 2019;52:397–402.
30. Ma Y, Diao B, Lv X, et al. 2019 novel coronavirus disease in hemodialysis (HD) patients: report from one HD center in Wuhan, China. Available at: https://www.medrxiv.org/content/10.1101/2020.02.24.20027201v2. Accessed March 2, 2020.
31. Expert Team of Chinese Medical Association Nephrology Branch. Recommendations for prevention and control of novel coronavirus infection in blood purification center (room) from Chinese Medical Association Nephrology Branch. *Chin J Nephrol*. 2020;36:82–84.
32. Hwang S-J. Guideline for dialysis facilities during COVID-19 outbreak. Taiwan Society of Nephrology. Available at: https://tinyurl.com/yx3zc5up. Accessed March 16, 2020.