

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 raised concerns about a global pandemic. As of March 2, 2020, 88,948 cases of COVID-19 have been reported worldwide in 65 countries (and a cruise ship) and 79,842 in mainland China, with 3043 deaths worldwide (2915 deaths in mainland China).²

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 *Beta-coronavirus* genus.³

Previous coronavirus infections, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), 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, IP10, monocyte chemoattractant protein 1, MIP1A, 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, virological examination, and so forth).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 several 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

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Saraladevi Naicker¹,
Chih-Wei Yang²,
Shang-Jyh Hwang³,
Bi-Cheng Liu⁴,
Jiang-Hua Chen⁵ and
Vivekanand Jha^{6,7}

¹Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ²Department of Nephrology, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Taoyuan, Taiwan; ³Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; ⁴Institute of Nephrology, Zhong Da Hospital, Southeast University School of Medicine, Nanjing, China; ⁵Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; ⁶George Institute for Global Health India, UNSW, New Delhi, India; and ⁷Manipal Academy of Higher Education, Manipal, India

Correspondence: Vivekanand Jha, The George Institute for Global Health, 310-11 Elegance Tower, Jasola District Centre, New Delhi 110025, India.
E-mail: vjha@georgeinstitute.org.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 should 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. 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 ± 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 ± 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 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 RBD 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. 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 Nephrology³¹ and the Taiwan Society of Nephrology³² have recently developed guidelines for dialysis units during the COVID-19 outbreak. A summary of these guidelines is provided below.

- (i) 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.

- (ii) Information on travel, occupation, contacts, and clusters (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.
- (iii) 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.
- (iv) Group activities, including group rounds, group studies, and case discussions, should be minimized.
- (v) 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.
- (vi) 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.
- (vii) 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.
- (viii) Patients and accompanying persons should be given hands-free 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.
- (ix) 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.
- (x) Place of dialysis treatment: patients should continue HD at the original HD

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331	center and not change to another	387
332	center.	388
333	(xi) Dialysis shift and personnel: do not	389
334	change dialysis shifts and caregiver staff	390
335	to avoid cross-contamination and	391
336	infection. Minimize the relevant	392
337	contacts.	393
338	(xii) Patients who need vascular access sur-	394
339	gery should be screened for novel	395
340	coronavirus before the surgery. Opera-	396
341	tions on patients with confirmed or	397
342	suspected novel coronavirus infection	398
343	should be carried out in a designated	399
344	room with necessary protection for	400
345	medical staff.	401
346	(xiii) Transportation: public transport should	402
347	not be used. Patients should arrange	403
348	personal transportation and take fixed	404
349	transportation routes. Transport	405
350	personnel and escorts should wear	406
351	surgical-grade or N95 masks	407
352	throughout.	408
353	(xiv) All patients who have fever should be	409
354	screened for novel coronavirus infection	410
355	and should be given dialysis in the last	411
356	shift of the day until infection is	412
357	excluded.	413
358	(xv) Pass route for entering hospital and	414
359	dialysis unit: the pick-up and drop-off	415
360	points should not be shared with other	416
361	dialysis patients. Entering and exiting	417
362	with other patients at the same time	418
363	should be avoided. The route, mode,	419
364	and time of transport of dialysis	420
365	personnel should be fixed.	421
366	(xvi) Precautions in dialysis unit: patients	422
367	should not be in close proximity; treat-	423
368	ment and waiting areas should have	424
369	good air conditioning and ventilation to	425
370	remove droplet particles from the air.	426
371	(xvii) Designated care personnel: all personnel	427
372	involved in direct patient care should	428
373	undertake full protection, including	429
374	long-sleeved, waterproof isolation	430
375	clothing; hair caps; goggles; gloves; and	431
376	medical masks (surgical mask grade or	432
377	above). Hand hygiene should be strictly	433
378	implemented.	434
379	(xviii) Dialysis machine: equipment that may	435
380	come into contact with patients or	436
381	potentially contaminated material	437
382	should be disinfected according to	438
383	standard protocols.	439
384	(xix) If a newly confirmed or highly suspected	440
385	case of novel coronavirus infection in	441
386	dialysis centers is identified, disinfection	442
	should be carried out immediately.	
	Areas in close contact with these patients	
	should not be used for other patients	
	until cleared.	
	(xx) The medical waste from confirmed or	
	suspected patients with novel coronavi-	
	rus 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 <i>basic</i>	
	<i>quarantine</i> 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 accor-	
	dance with the above-mentioned	
	conditions.	
	In summary, COVID-19, a disease caused	
	by a novel coronavirus, is a major global hu-	
	man threat with a potential to turn into a	
	pandemic. Kidney involvement seems to be	
	frequent in this infection, and AKI is an in-	
	dependent predictor of mortality. The impact	
	of this infection in those with chronic kidney	
	disease has not been studied, and the man-	
	agement 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 pa-	
	tients and healthcare personnel taking care of	
	these patients.	
	DISCLOSURE	
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