Focus on Characteristics of COVID-19 with the Special Reference to the Impact of COVID-19 on the Urogenital System

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Abstract
Coronavirus disease 2019 (COVID-19) is a new infectious disease that first emerged in December 2019. It has infected more than 4,890,000 people in more than 200 countries. This virus can cause progressive respiratory symptoms and severe diseases such as organ failure and death. The complete genomic sequence of SARS-CoV-2 was determined after the virus's identification, and the sequence analysis showed that SARS-CoV-2 strains are genetically similar to SARS-CoV. Angiotensin converting enzyme II is an entry receptor for SARS-CoV-2, which is highly expressed in the kidney, so some patients had symptoms of kidney damage. Here we reviewed the current progress of COVID-19 and its urogenital manifestations. In this rapidly moving field, this review was comprehensive as of May 30, 2020.

Introduction
Coronavirus disease 2019 (COVID-19) first emerged in late 2019 and has spread to more than 200 countries. Within 5 months, more than 4,890,000 people were infected with COVID-19. The number of new cases within 24 hours was more than 100,000. Because the sequence identity between this coronavirus and severe acute respiratory syndrome (SARS)-like betacoronavirus is about 87%, the World Health Organization (WHO) named this new coronavirus SARS-CoV-2. COVID-19 is mainly characterized by high fever (> 38°C, 78%), cough (76%), myalgia (44%), and dyspnea (55%) [1]. RT-PCR is widely used in the clinical diagnosis of COVID-19. WHO described the epidemic as a pandemic, suggesting that the speed and scale of transmission was not what we would expect. This is the first pandemic sparked by a coronavirus. Moreover, WHO urged that all countries should take a comprehensive approach based on their epidemic, and they must achieve a great balance between protecting health, preventing economic and social disruption, and respecting human rights.

Here, we reviewed the molecular features of SARS-CoV-2 and its receptor information. In addition, we described the epidemiological features and clinical complications of COVID-19 for further research.

Molecular Features of SARS-CoV-2
Coronaviruses have caused serious health problems over the past 20 years. Severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus in 2012 infected about 8,000 and 2,000 people, respectively [2]. SARS-CoV has
4 genera: Alpha-, Beta-, Gamma-, and Delta-coronavirus. SARS-CoV, SARA-CoV-2, and Middle East respiratory syndrome coronavirus are beta-coronavirus.

The genomes of coronaviruses are composed of a 5’ non-coding sequence, polymerase complex ORF1ab; S; ORF3a, b, c; E; M; ORF6; ORF7a, b; ORF8; ORF9a, b, c and 3’ terminal non-coding region, and a poly A tail [3]. The spike protein (S protein), which is the largest structural protein in coronaviruses, contains an N-terminal extremity (S1) and a C-terminal extremity (S2) [4] and the function of S protein is to help virus entry. The external subdomain of S1 subunit receptor binding domain (RBD) of SARS-CoV-2 shares around 40% amino acid sequence identity with other SARS-related coronaviruses, and the core part of RBD is highly conserved. Also, researchers [5] found a novel short putative protein with 4 helices in the ORF3b domain of SARS-CoV-2, which may be important for viral replication (current ongoing study).

Angiotensin converting enzyme II (ACE2) is a monokarboxypeptidase mediating angiotensin peptide metabolite, and is capable of cleaving angiotensin II to generate its active form. Some studies have confirmed that ACE2 is an entry receptor for the SARS-CoV. Remarkably, the core domain of RBD in SARS-CoV-2 is very similar to SARS-CoV, and this suggests that ACE2 may also be the receptor of SARS-CoV-2 [6] and the cellular serine protease TMPRSS2 prime SARS-CoV-2 for infecting target cells [7]. Zhou et al. [8] conducted virus infectivity experiments where HeLa cells expressed or did not express ACE2 proteins, and confirmed ACE2 as the receptor of SARS-CoV-2. The high-resolution structures of full-length ACE2 in SARS-CoV-2 were elucidated, suggesting 2 S protein trimers tightly bound on an ACE2 dimer and some variants in SARS-CoV-2 S protein could result in a tighter association between the RBD and ACE2. Another study showed that SARS-CoV-2 had higher affinity with the ACE2 receptor than the SARS-CoV S protein, and the specific monoclonal antibody of SARS-CoV S did not have effective affinity with SARS-CoV-2 S [10].

### Epidemiological Features

In patients infected with SARS-CoV-2, males are more often infected than females. The median age of patients is around 50 years and SARS-CoV-2 affects relatively few infants and children. The youngest COVID-19 patient is a neonate whose mother infected with SARS-CoV-2, which suggested the possibility of SARS-CoV-2 transmission via placenta [11].

The most typical symptoms are fever and cough, such as other pneumonia (table 1). We do not have prior serological evidence of infection in humans about SARS-CoV-2 [12]. Existing experimental evidence suggests the origin of SARS-CoV-2 may be bats [6]. This hypothesis is strengthened by studies that 49% of COVID-19 patients in the early stage of the epidemic had been exposed in the Huanan seafood market (a market for wildlife) [13]. Human-to-human transmission of COVID-19 has been officially reported in China, USA, and Canada. More notably, 4 COVID-19 patients who had been discharged (absence of clinical symptoms and abnormalities in chest computed tomography (CT) images and two repeated negative RT-PCR test results) had a repeated RT-PCR test 5 to 13 days later and all results were positive, suggesting that patients who have recovered may be carriers [14]. SARS-CoV-2 RNA could be detected in feces of COVID-19 patients and might transmit vertically via the fecal-oral route [15].
Clinical Characteristic and Diagnosis

COVID-19 is mainly characterized [1] by high fever, cough, sore throat, shortness of breath, fatigue, rhinorrhea and dyspnea. Compared with general pneumonia, these symptoms are not specific. The patients of SARS-CoV-2 infection had neurologic manifestations [16], such as myalgia, dizziness, anosmia and ageusia [17]. Some had digestive symptoms, such as diarrhea. The majority of patients on admission presented with non-specific symptoms and few patients were asymptomatic [18]. The pregnant women infected SARS-CoV-2 had same symptoms as adult patients and one thirds of their neonates were infected with SARS-CoV-2 [19]. Some neonates and children had atypical symptoms. Renal transplantation recipients infected with SARS-CoV-2 had more proportion of moderate and severe disease. Renal transplantation recipients with COVID-19 appeared to have worse clinical outcomes [20].

Current diagnosis of COVID-19 relied on the experience that the patients were at high-risk exposures, repeated positive pathogenic evidence, and clinical manifestations. It is notable that false-negative test of PCR assays results can occur [21]. Pathogenic evidence included the nucleic acid amplifications of SARS-CoV-2, genomic sequencing which is homologous with SARS-CoV-2, and specific IgM or IgG (+) of SARS-CoV-2 in blood. Besides, the differential diagnosis of COVID-19 included upper respiratory infection that caused by other virus, other pneumonia and non-infectious diseases, such as dermatomyositis.

Complications

Urogenital Injury

Studies on blood samples from 136 COVID-19 patients showed that blood urea nitrogen and serum creatinine were increased in 4.4 and 6.6% of patients, respectively. Moreover, 2.1% of COVID-19 patients had acute kidney injury. Jian’s study also found 2.5% of COVID-19 patients had renal function damage, one of which was serious (urea 26.5 mmol/l; creatinine 1,054.4 mmol/l) [22]. Related renal damage in COVID-19 patients were thought to be associated with the ACE2 receptor. The expression level of ACE2 was high in renal tubular cells and testis using the method of immunohistochemistry and next-generation sequencing.

There was not enough evidence to show that testis and prostate of patients could be infected. So far, no reports or guidelines showed the impact of novel coronavirus on sexual function and semen quality in patients.

Cardiac Injury

Cardiac injury is diagnosed by cardiac biomarkers (eg. troponin I), electrocardiography, and echocardiography. There were 20% patients had acute cardiac injury in Huang’s study [1]. It is worth noting that some patients had underlying cardiac diseases. TnT and NT-proBNP levels of COVID-19 patients changed dynamically during their hospitalization. TnT and NT-proBNP levels significantly increased among critical and fatal patients, but there was no significant change in TnT and NT-proBNP levels in survivors [23]. Therefore, myocardial injury had a significant association with the prognosis of COVID-19 patients. The myocardial injury may arise from the release of inflammatory cytokines and severe immune responses. Autopsies in case reports of COVID-19 patients showed inflammatory infiltrates (many macrophages) [24].

Cytokine Storm Syndrome

Current evidence shows that many COVID-19 patients have cytokine storm syndrome, but the incidence of such events is unclear. COVID-19-related cytokine storms are characterized by hyperinflammation and increased inflammatory factors, such as interleukin 2 and 7, monocyte chemoattractant protein 1, tumor necrosis factor-α, inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, and interferon-γ [25]. Hydroxychloroquine and convalescent plasma from COVID-19 patients may have immunomodulatory and anti-inflammatory effects.

Radiographic Findings and Laboratory Examination

Chest CT of most patients (also including asymptomatic patients) on admission showed abnormalities [26]. More than half of patients had two or more lobes involved. The features of non-contrast enhanced chest CT were multiple peripheral patchy ground glass opacities in bilateral multiple lobular [18]. About two thirds of patients had ground glass opacification. Half of patients had combined linear opacities and one third of patients had interlobular thickening. Besides, few patients showed air bronchogram sign.

Repeated positive nucleic acid amplifications test have been validated as confirming test of COVID-19. Many of these molecular assays are currently being vali-
dated in other laboratories. A part of cases diagnosed via throat swab specimens were positive for SARS-CoV-2 RNA in blood, urine [27], feces, and saliva [11] specimens. SARS-CoV-2 RNA (+) in urine samples showed the possibility of fecal/urine-respiratory transmission [27]. A study [15] found that stool specimens of many COVID-19 patients were positive for SARS-CoV-2 RNA, which were not associated with the presence of gastrointestinal symptoms. D. Paoli’s study showed that they did not find the SARS-CoV-2 RNA in the semen sample. Their results indicated that the virus may never be present in semen or the virus had been cleared by immune system [17]. But we stay alert with the possibility of transmission by semen because there is evidence about the orchitis and germ cell destruction (widespread germ cell destruction, few or no spermatoozoon in the seminiferous tubule and thickened basement membrane) in SARS-CoV patients [28].

One emphasis of discussion is the viral load and the viral duration in different body fluids, compared with respiratory swabs. Viral load in urine and feces of some adult patients were low but detectable. Some cases reported that SARS-CoV-2 detection by RT-PCR were negative in urine, stool or plasma of some COVID-19 patients with severe illness [29]. Viral load in feces sample of a neonate case was high from 6 to 18 days after onset, while virus load in plasma decreased [21]. Besides, SARS-CoV-2 RNA of the feces was reported a longer period of viral clearance than respiratory swabs [30,31]. The median viral duration in stool samples (22 days) was significantly longer than in respiratory (18 days) and serum samples (16 days) [31]. Moreover, the more severe the illness is, the longer the median duration of virus in patients will be. Types and timeliness of antiviral drugs were not important factors in affecting viral load and duration [31].

The researchers observed lower of lymphocyte counts and higher levels of interleukin-6, C-reactive protein and erythrocyte sedimentation rate in COVID-19 patients [15,32]. Then, the index about kidney function remained normal [32]. Mean lymphocyte count is $0.9 \times 10^9/L$, which is lower than normal range $(1.1–3.2 \times 10^9/L)$. Increased D-dimer, lymphopenia and prolonged prothrombin time (12.8 s) at admission were major blood features. The average of renal term (blood urea nitrogen and creatinine), liver term (lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase and total bilirubin) and heart term (creatinine kinase and creatine kinase-MB) were in the normal range [33]. In all COVID-19 patients on admission, survivors have lower neutrophil counts, higher platelet count, lower D-dimer level compared with non-survivors [33].

### Treatments

Except for the general treatment, this section introduced the clinical management of COVID-19 patients according to the manifestations of their illness. Notably, there are no Food and Drug Administration (FDA)-approved drugs for the treatment of COVID-19 [21].

### General Considerations

If patients have comorbidities, the treatments will be given upon the symptoms. Because patients may be facing cases of coinfections with hospital-acquired pneumonia and ventilator-associated pneumonia, NIH suggested routinely using the broad-spectrum empiric antimicrobial therapy [21]. But the Chinese guidelines of COVID-19 think we should not routinely use the broad-spectrum antimicrobial therapy.

### Antiviral Treatment

No proven effective drugs for SARS-COV-2 currently exist. But there are interferon-α, Remdesivir, Ribavirin, Oseltamivir, chloroquine, hydroxychloroquine and Lopinavir used in the clinical treatment. It is not recommended to use more than 3 antiviral drugs at the same time.

### Antithrombotic Treatment

There are some change of coagulation markers in COVID-19 patients, such as higher D-dimer levels and prolonged prothrombin time. Antithrombotic treatment should not be used to prevent thrombosis. Unfractionated heparin, low molecular weight heparin, and warfarin were frequently-used antithrombotic drugs in clinical treatment.

### ACE Inhibitors and Angiotensin Receptor Blockers (ARBs)

When patients have comorbidity of cardiovascular disease, the panel recommends using ACE and ARBs drugs. Because ACE2 is the cellular receptor of SARS-COV-2, ACE inhibitors may be wonder drugs for COVID-19. However, no existing evidence shows that ACE inhibitors or ARBs affected the risk of COVID-19 [34].

### Renal Failure

Seeking the reasons of renal failure is urgent for the patients with severe disease. The treatment focus on fluid
balance, acid-base balance and water and electrolyte balance. Critical patients could choose the continuous renal replacement therapy.

**Immune-Based Therapy**

Immune-based therapy includes COVID-19 convalescent plasma, SARS-CoV-2 immune globulins, interleukin-1and -6 inhibitors.

There are no enough scientific data to recommend for or against using this treatment to guide management decisions. Therefore, it is urgent to integrate the clinical data of COVID-19 and perform the clinical trials.

**Conclusion**

Research methodologies of SARS-CoV-2 have significantly improved in a short time, compared with SARS in 2002. Of course, the research in SARS set an example for novel coronaviruses. The outbreak of SARS-CoV-2 led us develop a rapid therapeutic and diagnostic approach for novel infectious disease. When SARS and MERS swept the world within 20 years, we did not pay enough attention to the epidemic unlike SARS-CoV-2 where we turned the tide on this virus in the early stage of the outbreak. Some antiviral drugs (for example, Remdesivir and chloroquine) could inhibit the growth of SARS-CoV-2 in vitro, but failed to take effect in patients. One of the biggest problems in clinical practice is the lack of effective drugs. Therefore, the current desideratum is not merely reliable rapid pathogen detection in the present but development of a clinical vaccine and antiviral drug. Besides, the urinary system is affected because of hypo-perfusion or drugs. The next step is to focus on the protection of urinary system in COVID-19 patients and the special treatment of COVID-19 patients with renal comorbidity.

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