The need for urogenital tract monitoring in COVID-19

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Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2, which invades a cell through binding to the ACE2 receptor and TMPRSS2 priming. Patients with severe disease predominantly present with pneumonia-related symptoms. However, evidence suggests that COVID-19 infection also has implications for the urogenital tract. Thus, urogenital organs should be considered when treating COVID-19.

> AKI in patients with COVID-19 might be a crucial negative prognostic factor for survival

In December 2019, a series of patients with symptoms resembling viral pneumonia presented in Wuhan, Hubei province, China; however, the cause of this disease was unknown and it spread rapidly throughout China. It was eventually identified as a novel coronavirus on 8 January 2020 by The Chinese Centers for Disease Control and Prevention. This novel coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting disease termed 2019 novel coronavirus (2019-nCoV), which was changed to coronavirus disease 2019 (COVID-19), according to the WHO Coronavirus disease (COVID-2019) situation reports. As of 5 April 2020, >1.2 million cases and 64,606 deaths have been reported globally. SARS-CoV-2 is a betacoronavirus and disease symptoms resemble SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Most patients with severe COVID-19 present with pneumonia-related symptoms, but some patients with severe disease could develop serious urinary complications including acute kidney injury (AKI), which requires continuous renal replacement therapy (CRRT)[1]. Furthermore, male reproductive systems are vulnerable to infection; dramatic changes in sex hormones in patients with COVID-19 have been observed, suggesting gonadal function impairment[2]. Thus, understanding the mechanisms by which SARS-CoV-2 impairs the urogenital system and learning from previous experience of managing these complications are of great importance for proper treatment and rehabilitation planning.

Acute kidney injury

A retrospective study by Li et al.[1] involving patients with COVID-19 provides some insights into the effect of this infection on the kidneys and the importance of monitoring kidney function. Proteinuria was observed in 60% of patients on the first day of admission, suggesting that they had renal injury before or at the moment of admission. Elevated levels of serum creatinine (SCr) (>104 μmol/l for men and >84 μmol/l for women) and blood urea nitrogen (>8 mmol/l) were observed in 22% and 31% patients, respectively, during treatment. Furthermore, 28% of patients gradually worsened and were diagnosed with AKI. The mortality of these patients was 5.3-times higher than those without AKI. A previous study including 536 patients with SARS-CoV in Hong Kong in 2003 showed that 36 patients developed AKI after viral infection after a median of 20 days and 33 (91.7%) of them died[3]. These results indicate that development of AKI in patients with COVID-19 might be a crucial negative prognostic factor for survival. Li and colleagues[1] also showed that patients with severe COVID-19 are at increased risk of kidney impairment. The level of SCr in patients with severe COVID-19 was significantly higher than in those without severe disease ($P<0.001$), whereas patients with mild COVID-19 had higher SCr levels than patients with non-COVID-19-associated pneumonia ($P<0.01$). AKI requiring CRRT occurred in 7 of the 65 patients with severe disease, but in none of the other patients included in this study.

In another study, histopathological examination was undertaken on autopsy kidney samples from six patients with COVID-19 who had impaired renal function before their death[3]. Acute renal tubular damage (but not glomerular injury) was seen in all six patients and acute tubular necrosis, luminal brush border sloughing and vacuole degeneration were observed to varying degrees. Similar findings were also observed in autopsy kidney samples from patients with MERS-CoV infection[4], which showed degeneration of the renal tubules, including ectasia changes and necrosis, sloughing, and loss of brush surface in the proximal tubular epithelial cells. These results suggest that the renal tubules are a common target of infection. As SARS-CoV-2, SARS-CoV and MERS-CoV have similar pathogenicity, comprehensive analysis of kidney injury in patients with SARS-CoV or MERS-CoV should be undertaken to improve our understanding of the possible outcomes.

Pre-existing chronic kidney disease

Chronic kidney disease (CKD) might increase the risk of poor clinical outcomes in patients with COVID-19. A study including 116 patients with MERS-CoV using regression modelling showed that CKD was the best

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> the key factors that mediate SARS-CoV-2 pathogenicity are highly expressed in urogenital organs

parameter for predicting mortality[5]. Similarly, according to the Chinese clinical guideline for the management of COVID-19, the Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Version 7), older people with comorbidities including CKD have a poor prognosis when they are infected with COVID-19. Thus, populations with risk factors that increase the chance of mortality, such as CKD, should be protected against SARS-CoV-2 infection.

Effects on the testes

Viruses such as HIV, hepatitis B and C, mumps, Epstein–Barr and papilloma can cause viral orchitis and even lead to male infertility and testicular tumours[6]. One study in testis autopsy specimens obtained from six patients who died of SARS-CoV showed that this virus can induce orchitis[6]. Pathological results showed spermatogenic cell apoptosis, germ cell destruction, few or no spermatozoa in the seminiferous epithelium, thickened basement membrane and leukocyte infiltration in all six specimens. Thus, the testes could be affected by SARS-CoV-2. A recent study provides insights into impaired male gonadal function on SARS-CoV-2 infection[2]. This study showed that the testosterone to luteinizing hormone (T to LH) ratio in 81 patients with COVID-19 was dramatically decreased in comparison with 100 age-matched healthy counterparts (patients with COVID-19: 0.74; healthy men: 1.31, $P < 0.0001$). Serum T to LH ratio (as a predictor of male gonadal function) could be a potential marker of impairment of reproductive health by SARS-CoV-2 (REF.[2]).

Possible mechanisms

Consistent with SARS-CoV, SARS-CoV-2 viral nucleoprotein antigen has been observed to have expression restricted to renal tubular epithelial cells[7]. MERS-CoV particles have also been detected in renal proximal tubular epithelial cells in renal autopsy samples[4]. Surprisingly, SARS-CoV particles were identified in the epithelial cells of testicular seminiferous tubules and Leydig cells, providing direct evidence of viral testicular damage[8].

Molecular studies on mechanisms of coronavirus infection have shown that coronaviruses rely on the binding of viral spike proteins to cellular receptors and on spike protein priming by host cell proteases to enter a cell. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor for entry and the serine protease TMPRSS2 for spike protein priming[9]. ACE2, a negative regulator in the renin–angiotensin system, is highly expressed in the epithelial cells of renal tubules, seminiferous ducts of testis, adult Leydig cells, the adrenal gland and the prostate (see Related links). TMPRSS2 is highly expressed in the kidney, prostate, seminal vesicles and epididymis (see Related links). Both of the key factors that mediate SARS-CoV-2 pathogenicity are highly expressed in urogenital organs, suggesting that these organs could be susceptible to damage by this virus.

In attempting to contain viral infections, adaptive immune cells can directly or indirectly target renal parenchymal cells to promote injury to the kidney and loss of function[7]. The testis, in spite of its immune privileged status, cannot be isolated from the immune system. Leukocyte infiltration and $CD3^+$ T lymphocytes and $CD68^+$ macrophages in the interstitial tissue of the testes can produce interferons that inhibit steroidogenesis and production of testosterone[10]. Inflammatory cytokines that are locally or systematically produced by these cells can activate the autoimmune response, destroying the seminiferous epithelium, which leads to autoimmune orchitis[6]. High levels of cytokines following viral or bacterial infection, illness or injury can cause deterioration in spermatogenesis and steroidogenesis, adversely affecting fertility[10].

Conclusions

Clinical symptoms of COVID-19 predominantly present in the respiratory system, but particular attention should be given to urogenital manifestations and/or complications. Older people with CKD are at increased risk of severe infection and AKI is associated with high mortality. Thus, monitoring the kidney function of patients with severe COVID-19 is of great importance, and CRRT for protecting kidney function and cytokine removal for patients who are critically ill could be crucial to improving recovery. The blood–testis barrier does not protect against COVID-19 and abnormal expression of sex hormones could be a result of impaired gonadal function. After recovery from COVID-19, young men who are interested in having children should receive a consultation regarding their fertility.

1. Li, Z. et al. Caution on kidney dysfunctions of COVID-19 patients. Preprint at *medRxiv* https://doi.org/10.1101/2020.02.08.20021212 (2020).
2. Ma, L. et al. Effect of SARS-CoV-2 infection upon male gonadal function: a single center-based study. Preprint at *medRxiv* https://doi.org/10.1101/2020.03.21.20037267 (2020).
3. Chu, K. H. et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int.* **67**, 698–705 (2005).
4. Alsaad, K. O. et al. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection — clinicopathological and ultrastructural study. *Histopathology* **72**, 516–524 (2018).
5. Morra, M. E. et al. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. *Rev. Med. Virol.* **28**, e1977 (2018).
6. Xu, J. et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). *Biol. Reprod.* **74**, 410–416 (2006).
7. Diao, B. et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Preprint at *medRxiv* https://doi.org/10.1101/2020.03.04.20031120 (2020).
8. Zhao, J. M. et al. Clinical pathology and pathogenesis of severe acute respiratory syndrome [Chinese]. *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi* **17**, 217–221 (2003).
9. Hoffmann, M. et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* https://doi.org/10.1016/j.cell.2020.02.052 (2020).
10. Hedger, M. P. & Meinhardt, A. Cytokines and the immune-testicular axis. *J. Reprod. Immunol.* **58**, 1–26 (2003).

Competing interests
The authors declare no competing interests.

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GTEx portal (TMPRSS2): https://gtexportal.org/home/gene/TMPRSS2
Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Version 7): http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm
The Cancer Cell Line Encyclopedia (ACE): https://portals.broadinstitute.org/ccle/page?gene=ACE
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