REVIEW

Urological implications of SARS CoV-19

Vipin Tyagi, MBBS,[1] Ajay Kumar Sharma, MBBS,[2] Mahendra Bhandari, MD[3]

[1]Department of Urology and Robotic Surgery, Sir Ganga Ram Hospital, New Delhi, India

[2]Royal Liverpool University Hospital, Liverpool, United Kingdom

[3]Vattikuti Urology Institute, Henry Ford Hospital, Detroit, Michigan, USA

TYAGI V, SHARMA AK, BHANDARI M. Urological implications of SARS CoV-19. *Can J Urol* 27(3): 10205-10212.

Introduction: *The novel coronavirus disease 2019 (COVID-19), pandemic has afflicted > 3.3 million people around the world since December 2019. Though, more than 1000 publications have appeared in scientific journals addressing a plethora of questions, there is a considerable hiatus in understanding of the behavior and natural history of the virus and its impact on urology. Also, a modified approach is the need of hour in taking care of patients as urologists should safeguard their teams, families, and patients.*

Material and methods: *The authors have used guidelines from USA, Canada, UK, Europe and India for making recommendations to help urologist define their own policies that may have to be fine-tuned on the basis of continued and evolving challenges they would encounter and the local resources at their disposal.*

Results: *COVID-19 do effect genitourinary system from kidney to testis. The authors provide scientific basis to urologists to help identify patients by remote consultation who are likely to be harmed by coming to the hospital, and not to miss those who need hospitalization for diagnostic or therapeutic interventions. There is uncompromised need of specific precautions during surgery to safe guard the surgeon and his team along with the patient.*

Conclusions: *Urological operations during COVID-19 pandemic should be limited to emergency cases during the acute phase with an exit strategy planned in a staggered manner, based on the scientific risk stratification. Telemedicine (e-clinics or virtual clinics) would help achieve the goal of risk stratification.*

Key Words: urology, SARS-CoV-2, COVID-19, urological surgery

Introduction

By April 28, 2020, > 4 million patients around the globe have been infected by SRS-CoV-2, and of these, > 276,000 have died.[1] This pandemic originated in Wuhan, China in December 2019 as pneumonia of unknown etiology. World Health Organization declared, SARS-Cov-2 infection as a pandemic on March 11, 2020.[2] This virus exploits ACE-2 which is distributed in the lungs, upper respiratory tract, ileum, heart, kidney, and urinary bladder.[3] Urology patients, at higher risk, are: (a) immunosuppressed due to medications following kidney transplantation, and (b) those with blunted immune-competence due to malignancy or as a result of chemotherapy.[4] In China, 4.4% of the total deaths were reported to happen in healthcare workers.[5] The authors aim to define the recommendations based on COVID-19 guidelines from USA, Canada, UK, Europe and India, so that urologists can understand the scientific basis to fine-tune their approach to utilize their resources, already limited by the pandemic, to face a challenge that is evolving all the time.

Accepted for publication May 2020

Address correspondence to Dr. Mahendra Bhandari, Suite 700, 1000 Town Centre, South Field, MI 48075 USA

SARS-CoV-2 and Covid-19

SARS-CoV-2 is a single-stranded RNA virus, belonging to the coronavirus family comprising of 42 viruses.[6] These viruses infect humans, livestock, birds, bats, and other wild animals. Two of these have been responsible for zoonotic pandemics known as severe respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) in 2003 and 2012, respectively.[7] SARS-CoV-2 phylogenetically shares 75% and 50% identity with SARS-CoV and MERS, respectively.[6]

In the earlier stages, as reported from Wuhan, the incubation period is 5.2 days.[8] The human-human transmission happens through droplet inhalation following coughing and sneezing, touching fomites, and inhaling aerosol. The overall case fatality rate reported in China, was 2.3%. However, higher mortality was reported in patients with comorbidities: 6% in patients with hypertension, 7.3% in diabetes mellitus, 10.5% in cardiovascular disease, and 10.2% in patients aged ≥ 70 years.[9] The median time from the onset of symptoms to death was 11.5 day in patients aged ≥ 70 years and 20 days in younger patients. In Italy, the rate of critical illness requiring admission is 16% of hospitalized patients, which is higher than in China.[10] The median age was 59 years with a male preponderance (73%).[11]

Pathogenesis

The SARS-CoV2 virus exploits ACE-2 as the receptor and uses cellular transmembrane protease, serine 2 (TMPRSS2) to enter the target cells.[12] The spike protein on the viral surface binds to ACE-2 with 10-20 times the affinity of SARS-CoV-1.[13] This higher ACE-2 affinity may explain the higher predisposition for human-human transmission. Cell entry of SARS-CoV-2 is facilitated by endosomal cysteine protease cathepsins.[14] The SARS-CoV-2 infects ciliated cells leading to acute respiratory distress syndrome, that is potentially lethal. Its entry to the target cell is a tightly regulated multi-step process beginning with the binding to ACE2. TRMPSS2 is essential for spike protein priming, Figure 1.[15]

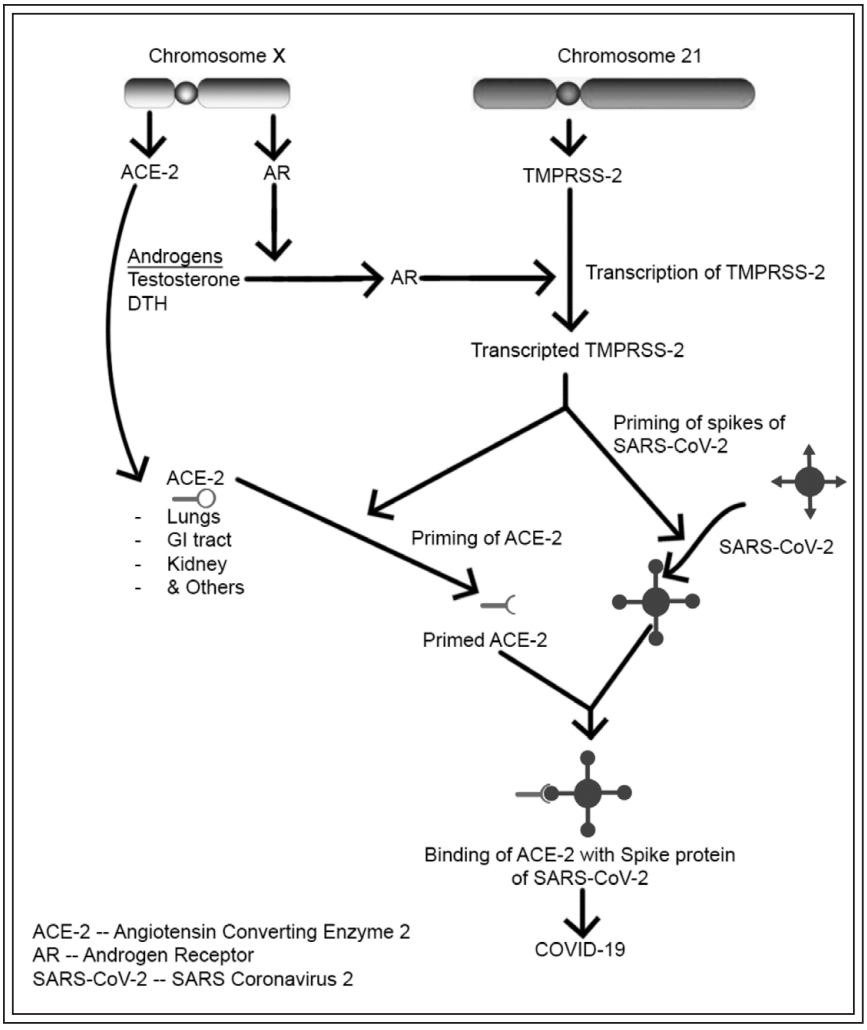

Figure 1. Pathogenesis of SARS-CoV-2.

Acute kidney injury (AKI)

ACE-2 levels in the kidney are nearly 100-fold higher than the lungs. AKI is reported in 5.1% of COVID-19 patients that increased to > 40% in hospitalized patients in Wuhan developed AKI in whom it was associated with higher mortality.[6] The etiology of AKI is multifactorial (a) cytopathic impact as evident by the finding of coronavirus fragments in the blood and urine of patients affected by SARS-1 virus in year 2003;[6] (b) the deposition of immune complexes of viral antigen-host antibody; (c) virus-triggered cytokine-storm resulting in hypoxia, shock, and rhabdomyolysis.[16] Novel biomarkers of acute tubular stress such as tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) by Nephro Check Test have been used for risk prediction.[17]

COVID-19 and reproductive system

The expression of ACE-2 has been identified in spermatogonia and Leydig cells of human testis in the patients who died due to COVID-19.[18] ACE-2 positive spermatogonia express a high number of genes associated with viral reproduction and transmission when compared to ACE-2 negative spermatogonia.[18] Acute orchitis can be caused by several members of the coronavirus family, including SARS-CoV-2.[19] Walter et al stated coronavirus (SARS-CoV-2) could be transmitted by semen.[20] The Society for Assisted Reproductive Technology, 2020 and the Centers for Disease Control and Prevention (CDC) issued warnings to avoid fertility programs involving males during the pandemic.[21,22] In Italy, a 2-week delay for sperm donation is advised for those who are at risk of contracting the SARS-COV-2 infection.[23] This advice needs to be viewed in light of the observation that none of the 34 patients (19% of them had acute orchitis) had evidence of COVID-19 virus in semen specimen taken at a median of 31 days of diagnosis.[24] The reproductive functions should be followed and evaluated in recovered COVID-2019 male patients for acute and chronic effects.

Androgens and COVID-19

COVID-19 is less common and severe in children. Eighty-two percent of 1591 patients were males as per Italian data of COVID-19 pandemic,[10] and higher androgens levels could be a possible explanation.[25] Goren et al observed a high frequency of male pattern hair loss among COVID-19 patients, suggesting that androgen expression may be a clue to COVID-19 severity.[26]

There are two possible mechanisms by which androgen can affect the course of COVID-19. Firstly, the regulation of TMPRSS-2, required for SARS-CoV-2 entry into target cells, depends on androgen receptor activity.[27-29] Secondly, androgen effect on immune system is suppressive, thus, resulting in more severe clinical course in males. TMPRSS2 is expressed on the prostate epithelium, and its expression is increased in prostate cancer tissue as compared with non-cancerous prostate tissue.[27] TMPRSS2 plays a crucial role in viral spread within the airway of murine models infected by SARS-CoV and MERS-CoV and in the resulting immunopathology.

In murine models infected by SARS virus and MERS virus, TMPRSS2 is reported to have a key role in virus dissemination of and resultant immunopathology.[30]

Urological surgery in COVID-19 era

During the pandemic, for the sake of safety of everyone, it is prudent to consider every urology patient as if he (or she) is infected by COVID-19. The following recommendations are worth highlighting.

Protective measures for the surgical team and first-line responders

The document issued by the Government of Canada comprehensively stipulates covering measures to be implemented by engineering teams, administrative staff and heath care workers.[31] Explicit guidelines have been circulated by the Royal College of Surgeons of England that recommend using NCEPOD classification of immediate, urgent, and expedited after discussing the real risk of proceeding and versus the expected risk of delaying a procedure.[32] The guidelines by the Government of Canada and those by the Royal College of Surgeons describe the steps that need to be implemented: (a) when an aerosol generating procedure is undertaken, and (b) when caring within 2 meter distance of COVID-19 patients and performing non-aerosol generating clinical procedures to save from viral transmission through fomites and fine droplets. [31,32] All the theatre staff and surgical team must be trained and supervised to use personal protective equipment (PPE). PPE consists of a face-fitting mask with filter, visor, water-proof plastic film underneath a gown impervious to fluids, and a long second layer of sterile gloves over the usual surgical gloves. The aerosol formation can happen during these phases: (a) endotracheal intubation, (b) operative surgery, (c) after the operation when disposing of the PPE, and (d) after leaving the OR.

By mid-April 2020, all the elective operations have been postponed all over the UK.[32] The guidelines by American College of Surgeons stress the need to use N95 respirators or respirators during any procedure that generates aerosol.[33] The guidelines from India as defined by the collaboration of three societies (Association of Minimal Access Surgeons of India, Indian Association of Gastrointestinal Endo Surgeons and Society of Endoscopic and Laparoscopic Surgeons of India) emphasize the need to stratify surgical patients on the basis of urgency, stress the need for multi-disciplinary approach and describe national guidelines to contain the transmission of COVID-19 in hospital setting.[34]

Hepatitis B virus and HIV has been identified in surgical smoke during laparoscopic surgery, and the presence of papillomavirus has been reported in the

vapors during laser treatment of warts.[35-37] Similarly, there is a risk of aerosol transmission of SARS-COV-2 during laparoscopy.[38,39] Therefore, these cases should be managed in a dedicated operation room (OR) with a negative pressure environment and separate access. The anesthetic machine must only be used for COVID-19 cases. If a dedicated OR is not available, all the postoperative cleaning protocols should be adhered to. The number of personnel in OR should be kept to a bare minimum. It is worth emphasizing that all the training programs should be suspended during pandemic, and the operative procedures should be performed by an experienced surgeon to minimize the utilization of medical resources.

The authors recommend using lowest intra-abdominal pressure for pneumo-insufflation to minimize leak of smoke or vapors. Power setting of electrocautery, ultrasonic scalpels, or electrothermal devices so that smoke or vapor formation is kept to minimum. Appropriate port size and minimum change of instruments would prevent leakage. Filters and a vacuum suction unit should be used for smoke evacuation. Gas evacuation at the end of operation should be achieved though desufflation on insufflator. The specimen be retrieved after all CO_2 gas is evacuated. Laparoscopic suture closure device should be avoided, and fascia should be closed after desufflation. Hand-assisted surgery can lead to significant leakage of CO_2 and smoke, thus should be avoided. During robotic surgery the console surgeon should wear goggles or sealed visor mask.[40]

Guidelines for the management of specific urological conditions

Risk stratification according to the nature of disease presentation and available resources

It is worth alluding to the European Guidelines that suggest dividing the patients into 4 groups: [41] (a) Emergency: is a life threatening situation presenting through an accident and emergency department; (b) High priority: if a definitive procedure is very likely if a procedure is postponed for > 6 weeks it will lead to disease progression, metastasis, loss of organ function or deaths; (c) Intermediate priority: clinical harm is possible if a procedure is postponed for 3-4 months but unlikely; (d) Low priority: these patients are unlikely to come to harm if a procedure is postponed for 6 months. Figure 2 shows an algorithm for a urology team to ensure the safety of patients, surgeons and the staff. Leia et al in their retrospective cohort study of 34 patients, who were unintentionally scheduled for elective operation during incubation period of confirmed COVID-19, reported that 44% of them needed ICU care and a mortality rate of 20.5%.[42] All 34 patients developed COVID-19 pneumonia shortly after surgery with abnormal findings on chest tomography.[42]

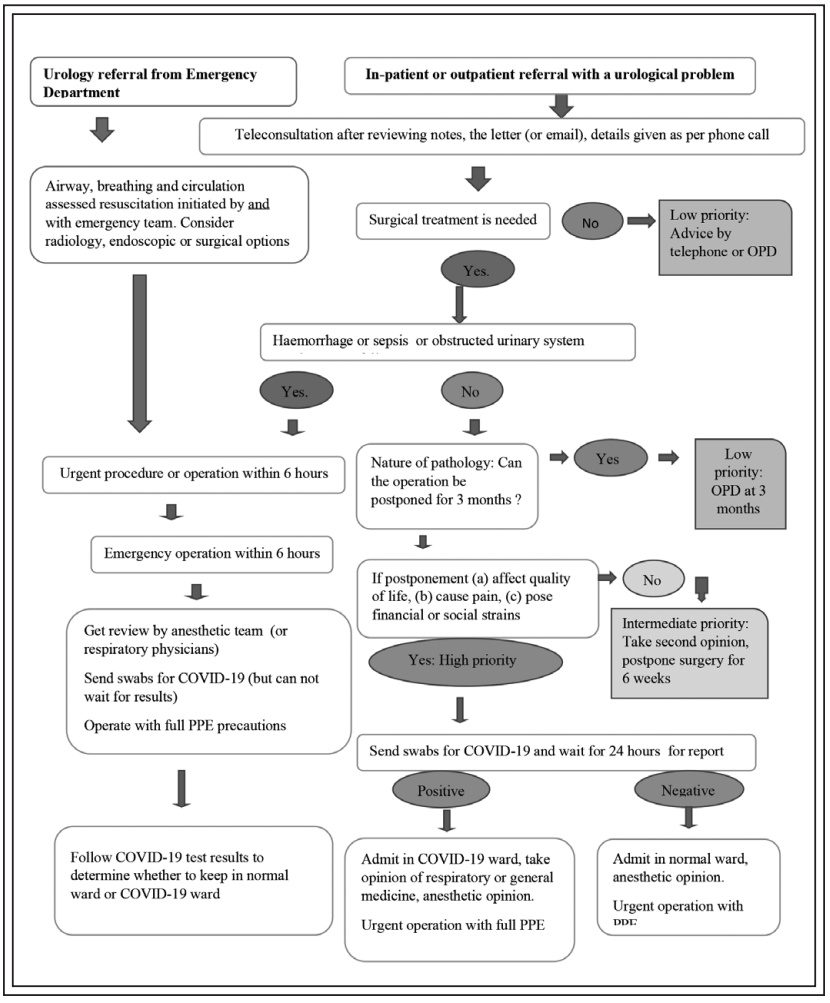

Figure 2. An algorithm for triage of urology patients during COVID-19 as adopted from the guidelines issues by American College of Surgeons, Canadian Government, Inter-Society Collaboration in India, Royal College of Surgeons of England, and European Urologists' Guidelines.

Urolithiasis

The patients with urolithiasis can be deferred unless presenting as an emergency. Fifteen percent of patients with urosepsis require ICU admission, with a mortality rate as high as 8%-10%.[43] An obstructed kidney or ureter should be decompressed by ureteric stenting.[44] Bedside ultrasound-guided percutaneous nephrostomy might be considered if necessary.[44] All the urinary diversion or stone related procedures should be done either under spinal or local anesthesia during this pandemic. General anesthesia with or without endotracheal intubation generates aerosol that has a high potential for spread of virus. Ureteric stenting with an external string is preferred as it can be removed on an outpatient basis.[44] An individualized pre-emptive one-time surgical (or interventional) approach is safer during pandemic rather than a medical option that may require admission in emergency. A ureteric stent can be left indwelling for 3-6 months though may get infected or blocked.[45] Standard sterilization procedures should be followed for usage of endourology instruments to avoid cross-contamination as this virus has been demonstrated in urine samples.[46]

Bladder outflow obstruction

A surgical treatment for benign prostatic hypertrophy (BPH) be deferred unless there is emergency e.g., prostatic abscess or massive haemorrhage.[47] Medical management should be preferred for BPH patients. Patients having acute retention of urine or chronic retention of urine should have a urethral catheter or suprapubic cystotomy.[48] Urethral stricture dilation and supra-pubic tube placement would have to stratified into either intermediate or low priority as per approach shown in Figure 2. Definitive surgery for bladder outflow obstruction would be placed in low priority.

Urogenital cancers

Renal cancer, urinary bladder cancer, and prostate cancer account for 2.2%, 3.0%, and 7.1%, of all cancers, respectively.[49] Cancer patients have 3.5-fold increase in the risk of COVID-19 related serious events.[50] Wang et al reported higher risk to cancer patients during COVID-19 pandemic because of insufficient medical support and older age.[51] The authors recommend risk-stratification or cancer patients.

Non-deferrable cancers: The patients with cancer cannot wait for pandemic to be over. This group includes: high-grade urinary bladder cancer or bladder tumors > 2 cm not invading into muscle, muscle-invasive bladder cancer or refractory carcinoma-in-situ, symptomatic renal tumours and those with caval involvement, high-grade upper tract urothelial carcinoma, high-risk or locally advanced prostatic carcinoma, penile cancer (that is > T1 and G3 lesion) adrenocortical cancer or highly suspected adrenocortical cancer, pheochromocytoma or paraganglioma which cannot be managed medically, testicular cancer, and post-chemotherapy retroperitoneal lymph node dissection.

Semi non-deferrable cancer: Cancer in which surgery should be considered in regions with a limited spread of COVID-19 or 3 months later in the regions that are significantly affected by pandemic. This includes intermediate disease or high-risk prostatic carcinoma with comorbidities, low-grade and small bladder tumors, renal tumor above stage T1b.

Other urological procedures:

All benign and reconstructive urology surgery be deferred until COVID19 pandemic is over. A prostate biopsy is the key to diagnose prostate cancer and should not be delayed when there is a possibility of high-risk disease. A shared decision be with the patient to commence palliative medical therapy even without the biopsy if there is strong evidence of metastatic disease. Prostatic biopsy shall be done with care as this virus has been identified in feces.[52]

Urological conditions that deserve urgent treatment are: testicular torsion, scrotal abscess, Fournier's gangrene, infection of a penile prosthesis, infected artificial sphincter, priapism, paraphimosis, severe phimosis, and urological trauma.

Issues concerning kidney transplantation and COVID19

Advice to transplant patients and their families

The governments in USA, Canada, Europe and UK recommended shielding of high-risk individuals (including transplant recipients) for 12 weeks.[53-55]

Monitoring of transplants

To minimize hospital visits, the patients are provided blood forms by post and given 3 months' supply of medication with tablets of various denominations just in case a change in dosage is needed.

Acute transplantation, to do or not to do

Most renal transplant departments discontinued living donor transplant program in mid-March 2020. In Liverpool the transplant activity was limited to low-risk (n = 5) cadaveric renal transplants (beneficial HLA matching, donors younger than 30 years and recipients younger than 30 years) were performed until the end of March 2020, wherein, simulect rather

than campath was preferred. All except two renal transplant centers have suspended their program.[56] All donors were screened for COVID-19 clinically and by testing. The recipients were asked about COVID-19 contact and were counselled about the risks and benefits. The reasons for this approach are: newly transplant patients are at maximum risk for 6 weeks, restricted availability of critical care beds, the lack of operating space as theatres are used to expand ITU facility, and to conserve PPE. In developing nations like India wherein a patient and family have travelled to a tertiary care hospital in a major city, it would be unaffordable to go back because of lack of dialysis facility in their home town, serious financial constraints made much worse by many weeks of 'lock-down'.

The risk to transplant patients

Just like any other viral illness, the transplant recipients are at high-risk of contracting COVID-19 and develop severe complications. The natural history of COVID-19 in transplant patients is unclear. They are advised to continue all their medications unchanged.

Local pathway for assessing a transplant recipient with suspected COVID-19

A transplant recipient with suspected COVID-19 infection causing dyspnoea or high fever, is advised to attend hospital. They should be using a mask and be placed in isolation away from other patients presenting with suspected COVID-19. There should be a close liaison between the infectious disease (ID) team and the transplant team for clinical assessment and management in accordance with pre-defined local protocols. It should be a senior clinician to take lead in examining the patient to minimize the traffic of people.[57]

The diagnosis and treatment of allograft dysfunction during COVID-19 pandemic?

For chronic allograft dysfunction the investigation (including biopsy) should be postponed until the COVID-19 epidemic is over. Acute dysfunction might be due to viral illness (AKI), secondary bacterial infection, or due to drug interaction. Although most acute rejection episodes do not present with painful graft or with fever, yet if it happens it may be difficult to distinguish this from COVID-19 illness. Investigations should include tests to identify viral (COVID-19, CMV, EBV, RSV, adenoviruses) or bacterial. Renal allograft biopsy is performed judiciously only after ruling out viral or bacterial infection because it would be unwise to raise the level of immunosuppression in the presence of an active infection if there is acute rejection.

COVID-19 patients who needed ITU admission had lower lymphocyte count, it is difficult to ascertain whether that was the cause or the effect. The presence of cardiovascular disease or diabetes in patients with COVID-19 pneumonia is associated with poorer outcomes.[58,59] Moreover, unpublished reports indicate that a BMI of > 35 is a significant risk factor for ITU admission.

A close cooperation between the ID team, the transplant team, and intensivists is crucial to avoid drug interactions when instituting anti-virals. Acute rejection of allografts might be a consequence of using beta interferon. Drug interactions of antibiotics (such as clarithromycin or fluconazole) with tacrolimus need to be kept in mind when planning treatment for secondary infections in COVID-19 patients. After recovery for ITU, the maintenance immunosuppression is carefully reintroduced to prevent acute rejection.

Reduction in immunosuppression

As in any viral illnesses in a transplant recipient, one should discontinue anti-metabolites (mycophenolate mofetil or azathioprine) when on cyclosporine or tacrolimus based dual or triple-drug maintenance immunosuppression. Zhang et al and Banerjee et al suggest reducing or omitting mycophenolate mofetil in renal transplant patients with mild COVID-19 disease based on their case series of 5 and 7 patients, respectively.[60,61] Although there are publications demonstrating the suppression of viral replication by tacrolimus, the beneficial effect has not been proven in vivo.[62]

Steroids should be converted to parenteral hydrocortisone if that patient cannot take it orally. One may have to increase the steroids by a factor of 3-5 times depending upon the severity of illness because a prolonged usage of steroids would blunt the pituitary-adrenal axis. For patients on mechanical ventilation, one may have to suspend all the immunosuppression temporarily, especially in the phase of viremia. Therapies such as steroids when instituted to counter the cytokine-storm in COVID-19 patients or giving hyperimmune globulin to fight viral replication by infusing plasma from donors who recovered from COVID-19, need to be taken into account when planning immunosuppression.[63] We need to be aware that a higher steroid dosage is known to be associated with prolonged viral shedding.[64]

Planning for staffing and followup of patients

Some clinicians and nurses may need to be reallocated their duties in other parts of the hospital, depending upon their skill set. There are staff members who would not be able to contribute to clinical work either

due to personal fitness (recovering from cancer or pregnancy), having to quarantine because of family members being COVID-19 positive, or because of child care issues due to closure of schools. These staff members can be given responsibilities that can be fulfilled remotely, such as responding to letters, emails, or phone calls. Telemedicine or telephonic calls (e-clinics or virtual clinics) would help achieve the 'shielding of transplant patients for 12 weeks. Elective clinical activity will need to be assessed individually and be discussed on with the patients on the phone for postponement.

Conclusions

Urological operations during COVID-19 pandemic should be limited to those patients with high grade cancers, trauma, bleeding, testicular torsion, or infected obstructed urinary system. Travel restrictions due to lock-down and the affordability of a major procedure in far-away city for a patient in a self-funding healthcare system such as in developing countries would need to be kept in mind when decision is being made to postpone until COVID-19 epidemic is over. All the benign urological surgery and operations for low-grade urological cancers should be postponed till the end of COVID-19 pandemic for the sake of patient safety and preserving the health and well-being of hospital staff. The resources are very limited during pandemic and thus to be used in cost effective and cost benefit manners. News reports have highlighted that limited resources during COVID-19 pandemic would have significant impact on patients with other diseases if the restrictions continue.[65,66] WHO is concerned that the patients suffering from other diseases (with a specific mention of malaria) are at a risk of missed diagnosis and delayed treatment.[67] Henceforth, there is dire need for defining and implementing an 'exit strategy' in a carefully orchestrated staggered manner that will be based on the scientific risk-stratification. An exit strategy would depend on some key indicators: reduction of transmission rate of COVID-19 virus to a consistent R_0 value of < 1 that has been between 2 to 3 for this virus, easy availability of reliable rapid testing of < 4 hours, health system well equipped with resources (man-power and PPE), and the identification of well-isolated and effectively segregated facilities in same hospital, and in the hospitals ear-marked for elective surgery. To begin with, the surgeons managing urology and transplant patients would choose low-risk patients with minimal comorbidities for surgical operations so that intensive care facilities, that are already overwhelmed, are not further strained. □

References

1. https://www.worldometers.info/coronavirus. Accessed 9th May, 2020.
2. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report 51. Accessed 9th May, 2020.
3. Xin Zou1, Ke Chen, Jiawei Zou et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020;14(2):185-192.
4. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020;21(4):e181.
5. Zahn M, Qin Y, Xue X, Zhu Shuajun Z. Death from COVID-19 of 23 healthcare workers in China. *N Engl J Med* 2020;April 15.
6. Lu R, Zhao X, Li J et.al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;6736(20):3025-3028.
7. Xu J, Zhao S, Teng T et al Systemic comparison of two animals to human transmitted human corona viruses SARS-CoV-and SARS-CoV. *Viruses* 2020;12(2):244.
8. Wu A, Peng Y, Huang B et al. Genome composition and divergence of coronavirus (2019 CoV) originating in China. *Cell Host Microbe* 2020;27(3):325-328.
9. Roser M, Ritchie H. Coronavirus disease (COVID-19). Our World in Data. 2020 available from: http://ourworlddataorg/coronavirus. Accessed 1st May, 2020.
10. Grasselli G, Zangrillo A, Zanella A et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV 2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020;323(16):1574-1581.
11. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506.
12. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (COVID-19) uses the SARS-1 coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *bioRxiv* 2020.
13. Wrapp D, Wang N, Corbett KS et al. Cryo-EM structure of 2019-nCoV spike in the perfusion conformation. *Science* 2020; 367(6483):1260-1263.
14. Zumla A, Hui DS, Azhar EI et al. Reducing mortality from 2019-nCoV: host-directed therapies. *Lancet* 2020;395(10024):e35-e36.
15. Xu X, Chen P, Wang J et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its Spike protein for risk of human transmission. *Sci China Life Sci* 2020;63(3):457-460.
16. Chan JFW, Lau SKP, To KKW et al. Middle East Respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARSlike disease. *Clin Microbiol Rev* 2015;28(2):465-522.
17. Zhao J, Zhou G, Sun Y. SARS coronavirus could cause multi-organ infection. *Med J Chinese People's Liberation Army* 2003;28:697-698.
18. Zhengpin Wang, Xiaojiang Xu. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, Leydig and Sertoli cells. *Cells* 2020;9(4):e920.
19. Xu J, Qi L, Chi X et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). *Biol Reprod* 2006:74(2):410-416.
20. Walter D. Cardona Maya, Stefan S et al. SARS-CoV-2 and the testis: similarity to other viruses and routes of infection. *Reprod Biomed Online* 2020 Apr 17. Epub ahead of print.
21. Center for Diseases Control and Prevention (CDC). Healthcare professionals: Frequently asked questions and answers. Https://www.Cdc.Gov/coronavirus/2019-ncov/hcp/faq.Html.
22. Society for Assisted Reproductive Tecnology. SART and ASRM issue advice for infertility patients concerning the novel coronavirus (COVID-19). Https://www.Sart.Org/news-and-publications/news-and-research/press-releasesand-bulletins/sart-and-asrm-issue-advice-for-infertility-patients-concerning-thenovel-coronavirus-covid-19/. Accessed 1st May, 2020.

23. La Marca A, Niederberger C, Pellicer A, Nelson SM. 2020. COVID-19: lessons from the Italian reproductive medical experience. *Fertil Steril* 2020; In Press.
24. Pan F, Xiao X, Guo J et al. No evidence of SARS-CoV-2 in semen of males recovering from COVID-19. *Fertil Steril* 2020.
25. Cai H. Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir Med* 2020;8(4):e20.
26. Goren A, Vaño-Galván S, Wambier CG et al. A preliminary observation: male pattern hair loss among hospitalized COVID-19 patients in Spain - A potential clue to the role of androgens in COVID-19 severity. *J Cosmet Dermatol* 2020 April.
27. Lucas JM, Heinlein C, Kim T et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. *Cancer Discov* 2014;4(11):1310-1325.
28. National Institutes of Health. TMPRSS2 transmembrane serine protease 2 [Homo sapiens (human)] Gene ID: 7113. Gene ID: 7113, updated on 13-Mar-2020. https://www.ncbi.nlm.nih.gov/gene/7113. Published 2020. Accessed 1st May, 2020.
29. Lin B, Ferguson C, White JT et al. Prostate-localized and androgen-regulated expression of the membrane- bound serine protease TMPRSS2. *Cancer Res* 1999;59(17):4180-4184.
30. Iwata-Yoshikawa N, Okamura T, Shimizu Y et al. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *J Virol* 2019;93(6):e01815-01818.
31. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/infection-prevention-control-covid-19-second-interim-guidance.html Accessed 9th May, 2020.
32. https://www.rcseng.ac.uk/standards-and-research/standards-and-guidance/good-practice-guides/coronavirus/covid-19-good-practice-for-surgeons-and-surgical-teams/.
33. https://www.facs.org/covid-19/clinical-guidance/surgeon-protection. Accessed 9th May, 2020.
34. http://www.selsi.in/ Inter association surgical practice recommendations in Covid 19 era. Page 1. Accessed 9th May, 2020.
35. Sawchuk WS, Weber PJ, Lowy DR, Dzubow LM. Infectious papillomavirus in the vapor of warts treated with carbon dioxide laser or electrocoagulation: detection and protection. *J Am Acad Dermatol* 1989;21(1):41-49.
36. Gloster HM, Roenigk RK. Risk of acquiring human papillomavirus from the plume produced by the carbon dioxide laser in the treatment of warts. *J Am Acad Dermatol* 1995;32(3):436-441.
37. Johnson GK, Robinson WS. Human immunodeficiency virus-1 (HIV-1) in the vapors of surgical power instruments. *J Med Virol* 1991;33(1):47-50.
38. van Doremalen N, Bushmaker T, Morris DH et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARSCoV-1. *N Engl J Med* 2020;382(16):1564-1567.
39. SAGES recommendations regarding surgical response to COVID-19 crisis - SAGES 2020 Available from: https://www.sages.org/recommendations-surgical-response-covid-19/#update.
40. ERUS (EAU Robotic Urology Section) guidelines during COVID-19 emergency. 2020 Available from: https://uroweb.org/wpcontent/uploads/ERUS-guidelines-for-COVID-def.pdf.
41. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Office-Rapid-Reaction-Group-An-organisation-wide-collaborative-effort-to-adapt-the-EAU-guidelines.
42. Leia S, Jiang F, Sua W et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(20)30075-4.pdf. Accessed on 8th May, 2020.
43. Fukushima H, Kobayashi M, Kawano K, Morimoto S. Performance of quick sequential (sepsis related) and sequential (sepsis related) organ failure assessment to predict mortality in patients with acute pyelonephritis associated with upper urinary tract calculi. *J Urol* 2018;199(6):1526–1533.
44. Proietti S, Gaboardi F, Giusti G. Endourological stone management in the era of the COVID-19: *Eur Urol* 2020:April.
45. Paick SH, Park HK, Oh SJ, Kim HH. Characteristics of bacterial colonization and urinary tract infection after indwelling of double-J ureteral stent. *Urology* 2003;62(2):214-217.
46. Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020;323(18):1843-1844.
47. Foster HE, Barry MJ, Dahm P et al. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline. *J Urol* 2018;200(3):612-619.
48. Ficarra V, Novara G, Abrate A et al. Urology practice during COVID-19 pandemic. *Minerva Urol Nefrol* 2020;March.
49. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.
50. Liang W, Guan W, Chen R et al. Cancer patients in SARSCoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21(3):335-337.
51. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020;21(4):e181.
52. Ling Y, Xu S-B, Lin Y-X et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl)* 2020;133(9):1039-1043.
53. https://www.gov.uk/government/publications/coronavirus-outbreak-faqs-what-you-can-and-cant-do/coronavirus-outbreak-faqs-what-you-can-and-cant-do Accessed 9th May, 2020.
54. https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-hcf.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhealthcare-facilities%2Fguidance-hcf.html Accessed 9th May, 2020.
55. Ti LK, Ang LS, Foong TW, Ng BSW. What we do when a COVID-19 patient needs an operation: operating room preparation and guidance. *Can J Anesth* 2020;67(6):756-758.
56. https://www.notifylibrary.org/sites/default/files/FR200320-Algorithm%20organs%20and%20tissues%20_%20third%20stage.pdf Accessed 9th May, 2020.
57. https://covid19.uwmedicine.org/Screening%20and%20Testing%20Algorithms/4%20-%20Immunocompromised%20Patients%20-%20Protocol.pdf Accessed 9th May, 2020.
58. Wang D, Hu B, Hu C et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061-1069.
59. https://tts.org/23-tid/tid-news/657-tid-update-and-guidance-on-2019-novel-coronavirus-2019-ncov-for-transplant-id-clinicians Accessed 9th May, 2020.
60. Zhang H, Chen Y, Yuan Q et al. Identification of kidney transplant recipients with coronavirus disease 2019. *Eur Urol* 2020;April.
61. Banerjee D, Popoola J, Shah S et al. COVID 19 infection in kidney transplant recipients. *Kidney Int* 2020:April.
62. Carbajo-Lozoya J, Muller MA, Kallies S et al. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. *Virus Res* 2012;165(1):112-117.
63. Su VC, Greanya ED, Ensom MHH. Impact of mycophenolate mofetil dose reduction on allograft outcomes in kidney transplant recipients on tacrolimus-based regimens: a systematic review. *Ann Pharmacother* 2011;45(2):248-257.
64. Ogimi C, Greninger AL, Waghmare AL et al. Prolonged shedding of human coronavirus in hematopoietic cell transplant recipients: risk factors and viral genome evolution. *J Infect Dis* 2017;216(2):203-209.
65. https://ecancer.org/en/news/17643-cancer-treatment-delays-could-increase-death-rates-due-to-impact-of-covid-19-pandemic-on-uk-hospital-capacity Accessed 1st May, 2020.
66. https://www.medicaleconomics.com/news/covid-19-fallout-how-will-other-needed-care-be-provided-during-pandemic.
67. https://www.who.int/news-room/q-a-detail/malaria-and-the-covid-19-pandemic Accessed 1st May, 2020.