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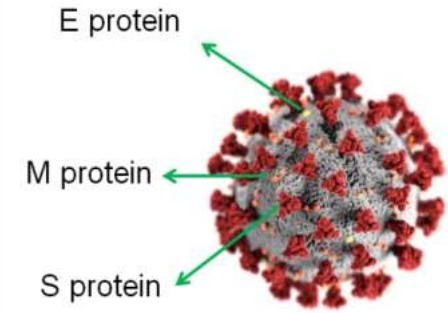
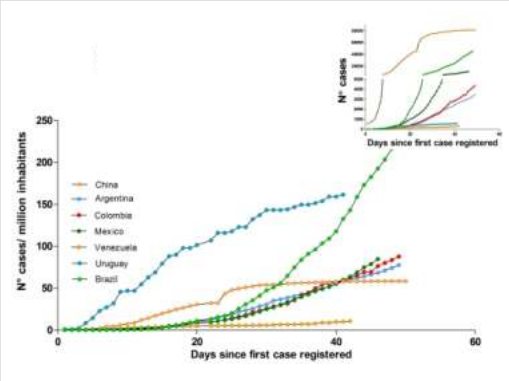
SARS-COVID-19 in Urology joint supplement of Brazilian Society of Urology (SBU) and American Confederation of Urology (CAU)



Ultrastructural morphology exhibited by coronaviruses. E protein, small envelope (E) protein; M protein, matrix (M) protein; S protein, spike (S) glycoprotein (homotrimer). Adapted from "Centers for Disease Control and Prevention (CDC)/ Alissa Eckert, MS; Dan Higgins, MAMS"



Transmission of SARS-CoV-2 in countries (China, Argentina, Colombia, Mexico, Venezuela, Uruguay, Brazil) which number of cases/million inhabitants is smaller than 500 (cumulative cases/ million inhabitants). The data used for the construction of the curves were obtained from the maps of John Hopkins University

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EDITORIAL
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SARS-COVID-19 transformed the world and urological practice

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SARS-COVID-19 pandemic changed the World and urological practice. The SARS-COVID-19 pandemic has a great impact in all medical fields and because the important changes in Urology in last 3 months and due to the large volume of information and articles received, we chose to carry out this supplement. Despite these extremely difficult times, we are very happy because this supplement marks the beginning of the partnership between the Brazilian Society of Urology (BSU) and the American Confederation of Urology (CAU). Soon the International Brazilian Journal of Urology has everything to become the official information Journal of CAU reinforcing the impact of the International Brazilian Journal of Urology on the American continent.

This Supplement presents original contributions with a lot of interesting papers about SARS-COVID-19 pandemic. The papers came from many different countries such as Brazil, USA, United Kingdom, Belgium, Colombia, Peru, Argentina, Germany, Netherlands, Italy, Spain, Canada, and China. As usual, the editor highlights some of them.

Dr. Lauxman and colleagues from Germany performed in page 6 (1) a nice explanation about the SARS-CoV-2 and COVID-19 outbreak and they observed that in most severe COVID-19 patients, the D-dimer level is significantly increased showing frequent clotting disorders and microthrombotic formations. This study is on the cover in this number.

Dr. Chen and colleagues from China performed in page 19 (2) a nice report about the Strategies and Management of Urological Diseases during the COVID-19 Pandemic in China and concluded that the patients seen by urologists are mostly elderly people, who are the frequent population suffering from severe diseases.

Dr. Esperto and colleagues from Italy performed in page 26 (3) an interesting report about the pandemic impact in Italy and concluded that COVID-19 emergency is a highly dynamic situation and the burden on the healthcare system varies daily according to the geographical region.

Dr. Sanchez and colleagues from Spain performed in page 50 (4) an important report about prostate cancer assistance during the COVID-19 pandemic and concluded that prostate biopsies should be delayed; androgen deprivation therapy allows us to defer definitive local treatment in many cases of intermediate and high risk prostate cancer and metastatic and castration resistant prostate cancer, combination therapies with abiraterone, apalutamide, darolutamide or enzalutamide could be considered. Chemotherapy, Radium-223 and immunotherapy are discouraged.

Drs. Zequi and Abreu from Brazil and Uruguay performed in page 69 (5) a nice report about the management of renal cell carcinoma (RCC) during COVID-19 pandemic and shows that in the pandemic COVID-19 times, a tailored risk-based approach must be used for a safe management of RCC, aiming to not compromise the oncological outcomes of the patients.

Dr. Casco and colleagues from Spain performed in page 86 (6) an important report about the therapeutic and surgical indications of patients with Penile Cancer in COVID-19 era and proposed an action protocol to facilitate decision-making, and concluded that in case of superficial non-invasive disease, topical treatment is effective in absence of lymph node involvement. In selected patients, radiotherapy is an organ-preserving approach with good results. Non-deferrable surgical treatment must be performed by an experienced surgeon

and as an outpatient procedure when possible. When indicated, the inguinal lymphadenectomy should not be delayed since it is decisive for patient survival.

Dr. Ibarra and colleagues from Spain Italy and Iran performed in page 104 (7) a nice review about the impact of the COVID-19 pandemic on sexual behavior in the population from three different countries: Iran, Italy and Spain from each country's perspective and concluded that in the upcoming months and years, we will be able to assess these effects in more detail, but we are sure that COVID-19 will have a negative impact not only in terms of affectivity but also in terms of sexual relationships. The impact of the coronavirus will be very important in the sexual life of the people and we will attend in the next months or years, to some changes in the relationships at all the levels.

Dr. Gonzalez and Ciancio from USA and Spain performed in page 145 (8) an important report about the risk factors, clinical presentation, therapeutic protocols, and outcomes of kidney transplantation recipients (KTRs) who become infected by SARS-CoV-2 and concluded that the ideal treatment for KTRs with SARS-CoV-2 infection remains unclear, and the answers regarding its optimal management still rely on expert opinion and long-term follow-up is required to better understand the prognosis and sequelae of COVID-19 in KTRs.

Drs. Zampolli and Rodriguez from Brazil and USA performed in page 215 (9) a nice report about the use of laparoscopy and robotics during the pandemic COVID19 and concluded that modifications of standard practices during minimally invasive surgery such as using lowest intra-abdominal pressures possible, controlled smoke evacuation systems, and minimizing energy device usage are recommended.

The Editor-in-chief expects everyone to enjoy reading of this supplement and for sure better times will come soon around the World.

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EDITORIAL COMMENT

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The Social, Economic and Sanitary Impact of COVID-19 Pandemic

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COMMENT

In the last 3 months, nearly a third of the world's population has changed their lifestyle. At this time of writing (June 30th) the COVID-19 pandemic has left a total of 10.302.867 confirmed cases, with more than 505.518 deaths worldwide, spreading to more than 188 countries (1). The pandemic has hit each of the different social strata, the population has had to re-adapt to the circumstances, absolutely all of us have changed the way we face the day to day.

Asia, Europe and recently Latin America have been involved in this catastrophe, where the delay in the implementation of health policies by governments has aggravated the problem.

Currently, Brazil, one of the main countries and economic force in Latin America, occupies the second place in the world with a total of 1.368.195 confirmed cases and 58.314 deaths (1).

The COVID-19 pandemic represents a sanitary, social and economic challenge at a global level, since the City of Wuhan in China declared it´s lockdown on January 23th 2020, about a third of the world's population has had to follow the same policies of restriction and isolation at home, imposed by governments, to reduce the spread of the disease to avoid the collapse the health system, measures that today are not entirely clear, as they have been implemented as "emergencies". This is the result of a lack of adequate epidemiological strategies, focused on the impact of the dissemination of the disease, with the application of tests to the population, tests that we do not currently have. Lockdown measures have led to the cessation of industrial and commercial production in most sectors, with job reductions and layoffs. Recently an editorial in the newspaper The Economist (2) revealed that approximately the cessation of economic activity produced by the lockdown and reduction of movement, will lead a total of 420,000,000 people to absolute poverty with incomes of less than USA $1.90 a day. If we look at first world countries, the United States (USA) has reported a gradual increase of 3.5% in unemployment in February versus 14.7% in April 2020.

The COVID-19 is without a doubt one of many pandemics that humanity has had to face throughout history. Never before has the fear of death been so pronounce, because we are reminded daily that people are dying in alarming numbers of around 100 deaths per minute and 150,000 deaths per day. This fear of loss, coupled with social distancing, lockdown, economic instability and uncertainty, will result in a strong psychosocial impact that will have to be addressed (3).

Regarding to international Health Systems, the impact on the cessation of development and stabilization in the coming months is enormous. It is estimated that England, by prioritizing care for COVID-19 patients and reducing care for cancer patients, within 6 months, will lose 40% of the quality of life gained in the last 5 years. The World Health Organization warns that if, as a result of the health impact of the pandemic, vaccination programs are paralyzed, around 140 children in Africa will die from each death caused by COVID-19. Just three months into lockdown, 10 months of discontinuation of Tuberculosis treatment in Third World countries will follow, equivalent to approximately 1,4000,000 deaths between 2020-2025.

Therefore, health systems require an adequate cost-benefit balance between the health policies and economic resources established in each country to face the pandemic, which must be directed on the basis of social risk groups, development dynamics, developmental heterogeneity and resources.

In most countries, the contingency and reaction plans established by the government have been misdirected, at the wrong time, implementing urgent measures, most of them with little effectiveness, we have faced a shortage of resources, lack of medical equipment, exhaustion with psychological burn out, infections of health care workers, how many of us have not suffered the disease and have seen so many colleagues infected?. Only in Spain the latest publication of the Spanish Ministry of Health (4) (June 12th 2020), has reported a total of 51. 849 infected health care workers.

Regarding the management of assistance protocols and triage, they have been constantly modified in each centre, in each province, trying to adapt to the resources and assistance demands of each country.

Without a doubt, all these experiences have enriched our knowledge, survival and management of the COVID-19 pandemic in each of our countries.

The volume of publications and scientific articles that have been written and made available is impressive. The medical community worldwide has joined efforts to be able to transmit quickly and effectively a large number of constant information from different medical specialties. The social networks have been overturned with the diffusion of information, which on some occasions, we could call misinformation.

In this context, urology, without a doubt, has not been the exception as since the end of March 2020, different International Urological Societies, have added their efforts to be able to establish recommendations, which have allowed us to optimize and prioritize patients´ care being implemented, in most Urology services. We have learned that patient care can continue, through the introduction of Telemedicine, that medical education is feasible and that we can share knowledge and with residents to continue their training.

At this time, we have shared academic sessions with our colleagues and friends around the world thus discovering these new tools of communication and development. We have also learned that we can grow among all, expanding our network of scientific collaboration, all these leaves us the COVID-19 Pandemic

As part of an international collaborative effort, the American Confederation of Urology (CAU) and Sociedade Brasileira de Urologia (SBU) performs this special edition, which aims to provide a screenshot impact of the COVID-19 Pandemic on Urology, within each different area of development It´s contains a total of 27 manuscripts performed by expert urologists from France, Italy, Spain, Iran, Germany, Argentina, Uruguay, Brazil, Mexico, Peru, Bolivia, Panama, the USA. The information that it contains, is reported until May 8th 2020.

Finally, I would like to thank each colleague participating in this project ,for the effort and valuable academic contribution, hoping that this crisis we are going through will allow us to grow as people and professionals. “Every crisis has a solution and a learning process, this only depends on us”

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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The SARS-CoV-2 Coronavirus and the COVID-19 Outbreak

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ABSTRACT

The SARS-CoV-2, a newly identified β-coronavirus, is the causative agent of the third large-scale pandemic from the last two decades. The outbreak started in December 2019 in Wuhan City, Hubei province in China. The patients presented clinical symptoms of dry cough, fever, dyspnea, and bilateral lung infiltrates on imaging. By February 2020, The World Health Organization (WHO) named the disease as Coronavirus Disease 2019 (COVID-19). The Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) recognized and designated this virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 uses the same host receptor, angiotensin-converting enzyme 2 (ACE2), used by SARS-CoV to infect humans. One hypothesis of SARSCoV-2 origin indicates that it is likely that bats serve as reservoir hosts for SARSCoV-2, being the intermediate host not yet determined. The predominant route of transmission of SARS-CoV-2 is from human to human. As of May 10th 2020, the number of worldwide confirmed COVID-19 cases is over 4 million, while the number of global deaths is around 279.000 people. The United States of America (USA) has the highest number of COVID-19 cases with over 1.3 million cases followed by Spain, Italy, United Kingdom, Russia, France and Germany with over 223.000, 218.000, 215.000, 209.000, 176.000, and 171.000 cases, respectively.

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INTRODUCTION

The coronaviruses (CoVs) are a family of enveloped positive-stranded RNA viruses broadly distributed among mammals and birds that cause respiratory and intestinal infections in animals and humans, and in some cases neurologic illness or hepatitis (1, 2). The CoVs have been the causative agent of two large-scale pandemics in the past two decades: 1) Severe acute respiratory syndrome (SARS) in 2002 and 2003 in Guangdong province, China (3, 4); and 2) Middle East respiratory syndrome (MERS) in 2012 in Middle Eastern countries (5, 6). After these two pandemic events, several pieces of evidence suggested possible future disease outbreaks: 1) CoVs undergo genetic recombination (7), which may lead to new evolving genotypes; 2) the presence of a large reservoir of

SARS-related coronaviruses (SARSr-CoVs) in horseshoe bats in China (8, 9); and 3) previous studies determined that some bat SARSr-CoVs have the potential to infect humans (2, 10-13).

The SARS-CoV-2, previously known as the 2019-novel coronavirus 2019-nCoV (14) (Figure-1), is a newly identified β-coronavirus that caused an epidemic of acute respiratory syndrome in humans, which started in December 2019 in the context of a seafood market in Wuhan, China (14). Later, in February 2020, The World Health Organization (WHO) named the disease as coronavirus disease 2019 (COVID-19). The COVID-19 has now progressed to be transmitted by human-to-human 'contact' and spread within few months not only throughout China but also worldwide, affecting over 4 million people and killing more than 279.000 of them in 187 countries as of May 10th 2020 (15). Typical clinical symptoms of COVID-19 patients are fever, dry cough, breathing difficulties, headache and pneumonia and in some cases gastrointestinal infection symptoms.

GENERAL CHARACTERISTICS OF SARS-CoV-2

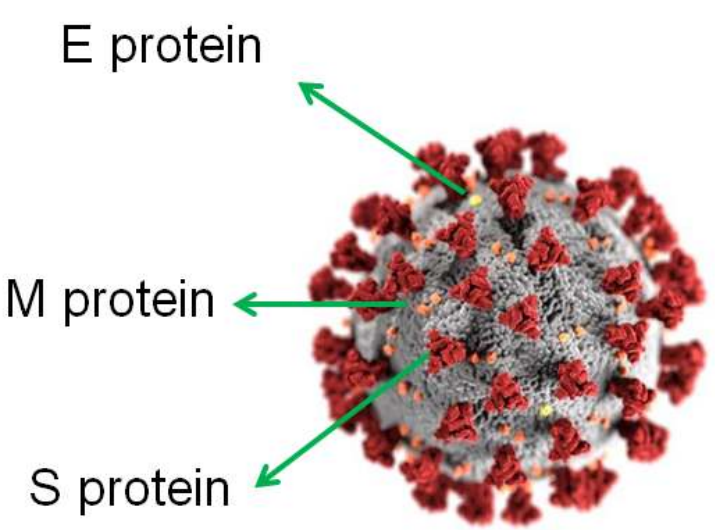
1 - Classification

The CoVs were previously classified based on serologic (cross-) reactivity involving the structural protein spike (S) glycoprotein until the classification shifted to comparative sequence analysis of replicative proteins (16, 17). The SARS-CoV-2 has been reported as the seventh coronavirus known to infect humans (14, 18). SARS-CoV, MERS-CoV and SARS-CoV-2, all β-CoVs, can cause severe respiratory disease in humans. The other four human CoVs, two α-CoVs HCoV-NL63 and HCoV-229E, and two β-CoVs HCoV-OC43 and HCoV-HKU1, cause mild respiratory symptoms (2, 13, 14). The SARS-CoV-2 clusters with SARS-CoVs in trees of the species *Severe acute respiratory syndrome-related coronavirus and genus Betacoronavirus* (14, 18, 19) (Figure-2). Based on phylogeny and taxonomy, the Coronavirus Study Group (CSG) of the ICTV recognized this virus as a sister to severe acute respiratory syndrome coronaviruses (SARS-CoVs) of the species *Severe acute respiratory syndrome-related coronavirus* and designated it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (19).

2 - Structure and Mechanism

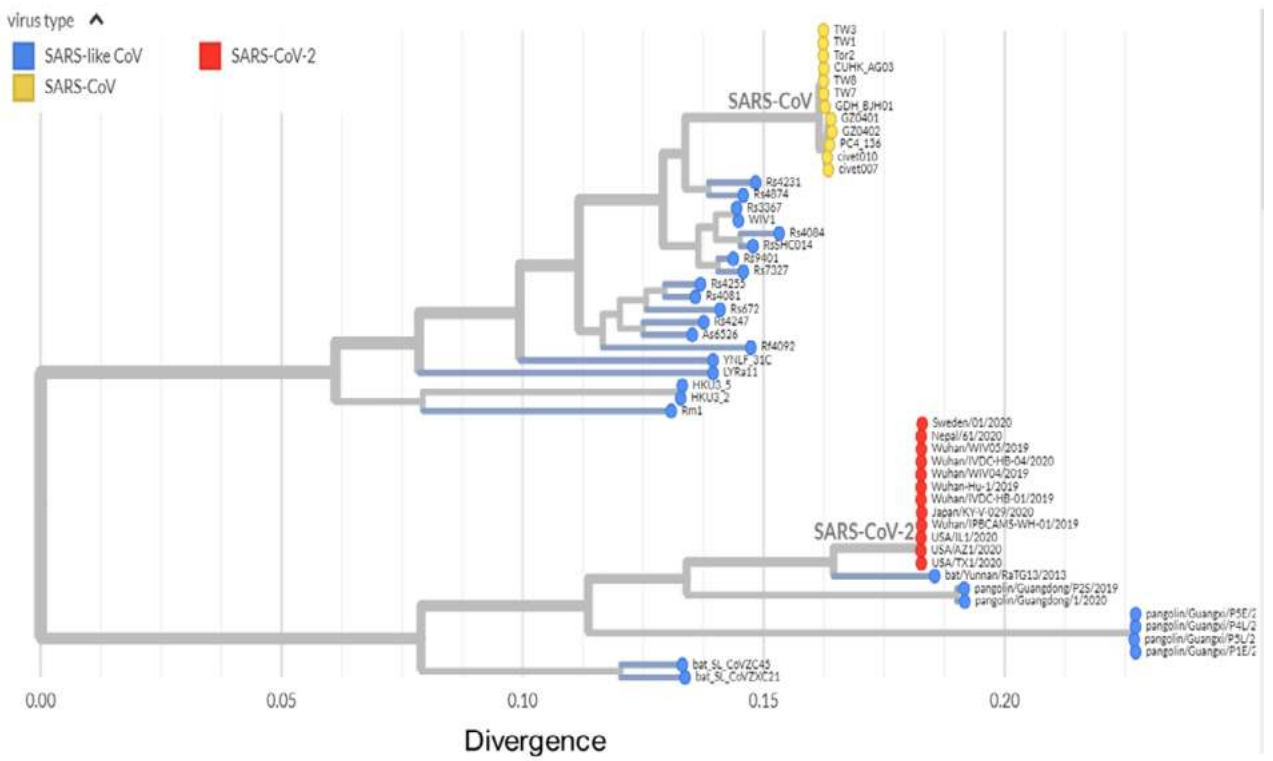
The first complete SARS-CoV-2 virus genome has been reported to be 29.9 kilobases (GenBank accession number MN908947) (18), which consists of six major open-reading frames (ORFs)

Figure 1 - Ultrastructural morphology exhibited by coronaviruses.



E protein, small envelope (E) protein; M protein, matrix (M) protein; S protein, spike (S) glycoprotein (homotrimer). Adapted from "Centers for Disease Control and Prevention (CDC)/ Alissa Eckert, MS; Dan Higgins, MAMS".

Figure 2- Phylogeny of SARS-like betacoronaviruses including novel coronavirus SARS-CoV-2.



Phylogenetic tree including 52 genomes. Red dots, SARS-CoV-2 coronaviruses from the COVID-19 epidemic; yellow dots, SARS-CoV coronaviruses from the 2002-03 SARS outbreak; and blue dots, SARS-like coronaviruses. Adapted from "github.com/blab/sars-like-cov"; "Built with blab/sars-like-cov and maintained by Trevor Bedford and Emma Hodcroft".

that are common to CoVs, and a number of other accessory genes (14, 18). Four ORFs of SARS--CoV-2 genome encode four essential structural proteins: (1) spike (S) glycoprotein (S1 and S2 subunits) that attaches to the host receptor through the receptor binding domain (RBD) (S1 subunit), determines the virus host range (S1 subunit), and mediates virus-cell membrane fusion (S2 subunit); (2) matrix (M) protein that mediates nutrients transport across the transmembrane, bud release and envelope formation; (3) small envelope (E) protein; and (4) nucleocapsid (N) protein which interfere with the host innate immune response (20) (Figure-1). The spike glycoprotein from CoVs forms homotrimers protruding from the viral surface and mediating the entry of the virus genome into the host cells (21). Therefore, it constitutes the main target of neutralizing antibodies after infection and hence, the focus of vaccine designing (22). Two structural acquisition of SARS-CoV-2 spike (S) glycoprotein have not been found in lineage B β-coronavirus: 1) a functional polybasic (furin) cleavage site at the junction between the S1/ S2 subunits which is cleaved during biogenesis; and 2) three adjacent predicted O-linked glycans (22). Curiously, the acquisition of polybasic cleavage sites in the hemagglutinin protein from low-pathogenic avian influenza viruses turns them into highly pathogenic forms (23). The introduction of the predicted O-linked glycans could build a 'mucin-like domain', like those found in Ebola and Marburg viruses, that shields select immunodominant epitopes on the SARS-CoV-2 spike protein (24). O-glycosylated 'mucin-like domains'

may physically hinder the interaction between virus-infected cells and immune cells (25).

The SARS-CoV-2 uses the same host receptor, angiotensin-converting enzyme 2 (ACE2), used by SARS-CoV to infect humans (14). ACE2 is a metalloprotease expressed in the cells of the lung, intestine, liver, heart, vascular endothelium, testis and kidney (2). In addition, the SARS-CoV-2 seems to have an RBD that binds with high affinity to ACE2 from humans and other species with high receptor homology (26). Six amino acids present in the RBD of the spike protein are essential for binding to host ACE2 receptors, and for establishing the host range of SARS-CoV-like viruses. Interestingly, five of these six amino acids differ between SARS-CoV-2 and SARS-CoV (26).

3 - Theories of SARS-CoV-2 Origins

It has been reported that MERS-CoV originated from bats, being dromedary camels the reservoir host triggering the spillover to humans (27). However, palm civets and racoon dogs have been indicated as an intermediate host for zoonotic transmission of SARS-CoV bridging bats and humans (28). In this sense, the intermediate host of SARS-CoV-2 remains unknown. Nevertheless, Ge et al. (9) proposed that some bat SARS-like coronaviruses (SL-CoVs) may directly infect human cells without an intermediate host. They were able to isolate a live bat SL-CoV (bat SL-CoV-WIV1, Figure-2) from bat fecal samples, which shares 99.9% sequence identity to Rs3367 (Figure-2), a bat coronavirus from Chinese horseshoe bats in Yunnan, China, and uses the ACE2 receptor from humans, civets and Chinese horseshoe bats for cell entry (9). Later in 2015, Menachery et al. (11) validated this hypothesis by synthetically producing an infectious recombinant virus from a bat coronavirus SHC014 (RsSHC014, Figure-2) that could efficiently replicate both *in vitro* in primary human airway cells, and in vivo in mouse lung. Thus, they emphasized the potential risk of SARS-CoV re-emergence from viruses currently circulating in bat populations without the necessity of an intermediate host (11).

Andersen et al. (29) have recently postulated two hypotheses that could explain the origin of SARS-CoV-2: 1) Natural selection in an animal host before zoonotic transfer; and 2) Natural selection in humans following zoonotic transfer. Regarding the first hypothesis, it is likely that bats serve as reservoir hosts for SARSCoV-2 (30, 31), since the genome sequence of SARS-CoV-2 shares a 96.2% identity at the whole genome level with that of bat CoV RaTG13 (14) (phylogenetic proximity in the clade SARS-CoV-2//bat/Yunnan/RaTG13/2013, Figure-2). Nonetheless, Wu et al. (18) reported that bats were not available for selling in the seafood market, where the first COVID-19 cases appeared (18). They found that the SARS-CoV-2 virus strain designated as WHCV (GenBank accession number MN908947) shares a nucleotide identity of 89.1% with bat SARS-like CoV isolated from bat (Bat-SL-CoVZC45- GenBank accession number MG772933) that had been previously collected from Zhoushan City, Zhejiang province, China, between 2015 and 2017 (32) (bat_SL_CoVZC45, Figure-2). Interestingly, the spike glycoprotein from some pangolin CoVs shows high similarity to SARS-CoV-2 in the RBD, which includes all six key RBD residues (33), supporting the existence of alternative intermediate host like pangolins, snakes and turtles (34), though not yet identified. This also indicates that all six key RBD residues may have been already present in the virus that jumped to humans (29). In terms of the second hypothesis, Andersen et al. (29) proposed that the genomic characteristics acquired from the progenitor of SARS-CoV-2, which would prime a pandemic outbreak, have taken place initially in humans during an undetected human-to-human transmission.

TRANSMISSION

The common transmission routes of SARS-CoV-2 include: 1) Direct exposure with cough, sneeze and droplet inhalation within a range of about 1.8 meters; and 2) Contact transmission through contact with oral, nasal, and eye mucous membranes (35). It has been also suggested that the SARS-CoV-2 transmission is not only limited to the respiratory tract (36), the eye mucosa may provide the virus with the portal to enter the body (32). Similarly, saliva may also directly or indirectly transmit SARS-CoV-2 (37). This is especially important during dental procedures, since aerosols and droplets mixed with patient's saliva and even contaminated blood with virus are genera-

ted (38). In similar way, Wax et al. (39) suggested that SARS-CoV-2 may be airborne through aerosols formed during medical procedures (39). In this sense, indirect contact via contaminated surfaces is another possible cause of infection. Interestingly, the presence of SARS-CoV-2 in fecal swabs (29%) and blood (1%) from infected individuals indicated the possibility of multiple transmission routes; however, no individuals contained detectable viral RNA in their urine (40). Additionally, it has been reported that contact with asymptomatic patients may represent another form of virus transmission (41). In this aspect, an epidemiological model published at the beginning of the outbreak in China suggested that subclinical infections may have been the source of a majority of infections (42).

International actions have been taken to reduce the social viral transmission by implementing "physical distancing" strategies, such as staying at least two meters apart from other people, not gathering in groups, considering delivery services, using cloth face cover to protect mouth and nose when around others or when going out in public, working from home when possible, avoiding the use of public transportation, implementing digital/distance learning. "Quarantine" has been employed to keep someone who might have been exposed to COVID-19 away from others, and "isolation" to separate sick people from healthy ones. Those actions have impacted on the viral transmission profile in those countries that followed the guidelines from the "Centers for Disease Control and Prevention" (CDC) (Figures 3A and B).

DISEASE PATHOPHYSIOLOGY AND THE IMMUNE RESPONSE

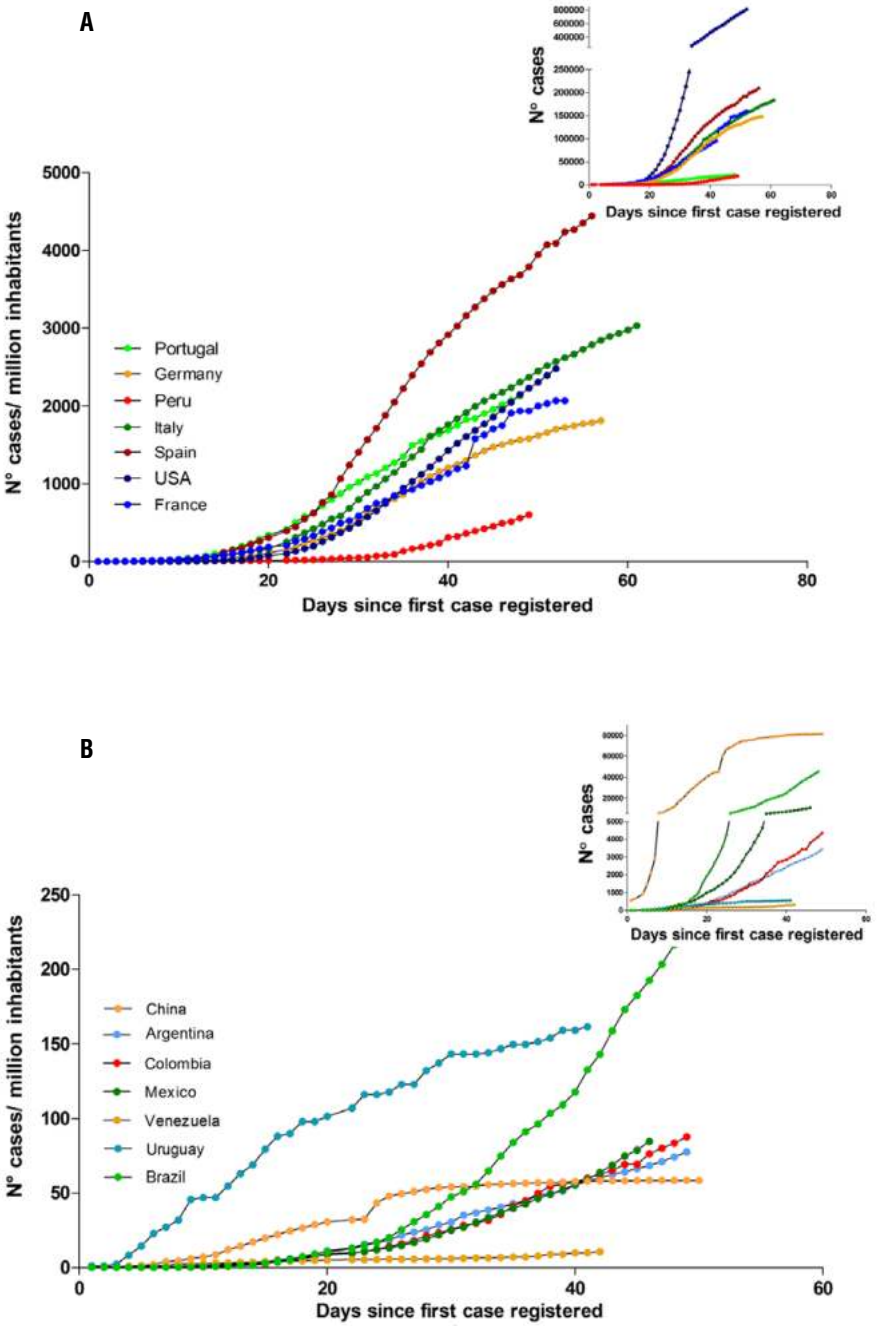
The clinical manifestations of COVID-19 range from mild to severe compromise, with few cases showing a fatal course. The most common reported symptoms are fever, cough, myalgia or fatigue, followed by pneumonia, and dyspnea, whereas less common reported symptoms include headache, diarrhea, and hemoptysis (43). Patients with mild symptoms were reported to recover after one week while severe cases experienced progressive respiratory failure due to alveolar damage, likely leading to death (43). Although the exact pathophysiological mechanisms underlying SARS-CoV-2 disease are not properly understood, genomic similarities to SARS-CoV may allow to infer the accompanying inflammatory response as being involved in the development of severe pneumonia (44, 45) (Table-1).

Histopathological observations of pulmonary lesions from SARS cases not only show nonspecific inflammatory responses such as edema and inflammatory cell infiltration but also a severe exfoliation of alveolar epithelial cells, alveolar septal widening, damage to alveolar septa, as well as alveolar space infiltration in a distinctly organized manner. SARS-CoV infection can cause pathological changes, degeneration, infiltration, and hyperplasia. Damage to the pulmonary interstitial arteriolar walls indicates that the inflammatory response plays an important role throughout the course of disease despite (or beyond) the pathogenic effect of Coronaviruses (46).

Even though SARS-CoV-2 is less lethal than MERS-CoV, up to 10-20%, people over 60 years and those with underlying medical co-morbidities, are more likely to develop a severe disease characterized by interstitial pneumonia and acute respiratory distress syndrome (ARDS) or even septic shock. Likewise, it is common to observe high levels of acute-phase reactants and features from the macrophage activation syndrome such as hyperferritinaemia, hepatic dysfunction and diffuse intravascular coagulation (44). Case definition guidelines consider symptoms like fever, decrease in lymphocytes and white blood cells, new pulmonary infiltrates on chest radiography, and no improvement in symptoms after 3 days of antibiotics treatment (43).

During a viral infection, the host mounts an immune response (IR) addressed to contain the infection. Recent advances in the knowledge of the innate IR against viruses point out that this type of IR inhibits virus replication, promotes virus clearance, induces tissue repair, while promoting a prolonged adaptive IR against the viruses. In most cases, pulmonary and systemic inflammatory responses associated with coronavirus are mediated by innate immune mechanisms upon virus recognition. However, an exacerbated IR also plays an immunopathogenic role, accounting for pulmonary tissue damage, functional impairment, and reduced lung capacity (43). The damaged cells induce innate inflammation in the lungs, largely mediated by proinflammatory macrophages

Figure 3 - SARS-CoV-2 transmission.



Number of cumulative cases per million of inhabitants: Both graphs (A and B) show the daily evolution of the number of detected cumulative cases of COVID-19 until 50 days after the first reported case normalized to each country's population. In the upper right boxes the absolute number of cases during the same time period is shown. **(A)** Transmission of SARS-CoV-2 in countries (Portugal, Germany, Peru, Italy, Spain, USA, France) which number of cases/million inhabitants is greater than 500 (cumulative cases/ million inhabitants). **(B)** Transmission of SARS-CoV-2 in countries (China, Argentina, Colombia, Mexico, Venezuela, Uruguay, Brazil) which number of cases/million inhabitants is smaller than 500 (cumulative cases/ million inhabitants). The data used for the construction of the curves were obtained from the maps of John Hopkins University https://coronavirus.jhu.edu/map.html (15).

Table 1- Summary of the symptoms recorded in 191 COVID-19 confirmed patients hospitalized in Jinyintan Hospital or Wuhan Pulmonary Hospital before January 31st, 2020 (45). (n= 191).

Fever (temperature >37.3°C)	Cough	Sputum	Myalgia	Fatigue	Diarrhoea	Nausea or vomiting
180 (94%)	151 (79%)	44 (23%)	29 (15%)	44 (23%)	9 (5%)	7 (4%)

and granulocytes. Such lung inflammation further emerges as the main cause of life-threatening respiratory disorders in severely ill patients (47) (Figure-4).

When a virus invades the host, the viral nucleic acid is initially recognized by Pattern Recognition Receptors, like Toll Like receptor 4 (TLR4) or Melanoma Differentiation Antigen 5 (MDA-5), that recognize S protein or nucleic acids, respectively. A signaling cascade is then activated to promote the synthesis of type I interferons (IFN-alpha and IFN--beta). Type I IFNs subsequently activate the downstream JAK-STAT signal pathway, promoting the expression of IFN-stimulated gene(s). As host's major antiviral molecules, IFNs limit virus spread, play a promoting role for macrophage phagocytosis of antigens, as well as Natural Killer (NK) cells restriction of infected target cells and T/B cells. It follows, that blocking the production of IFNs has a direct effect on the survival of the virus within the host (46) (Figure-4).

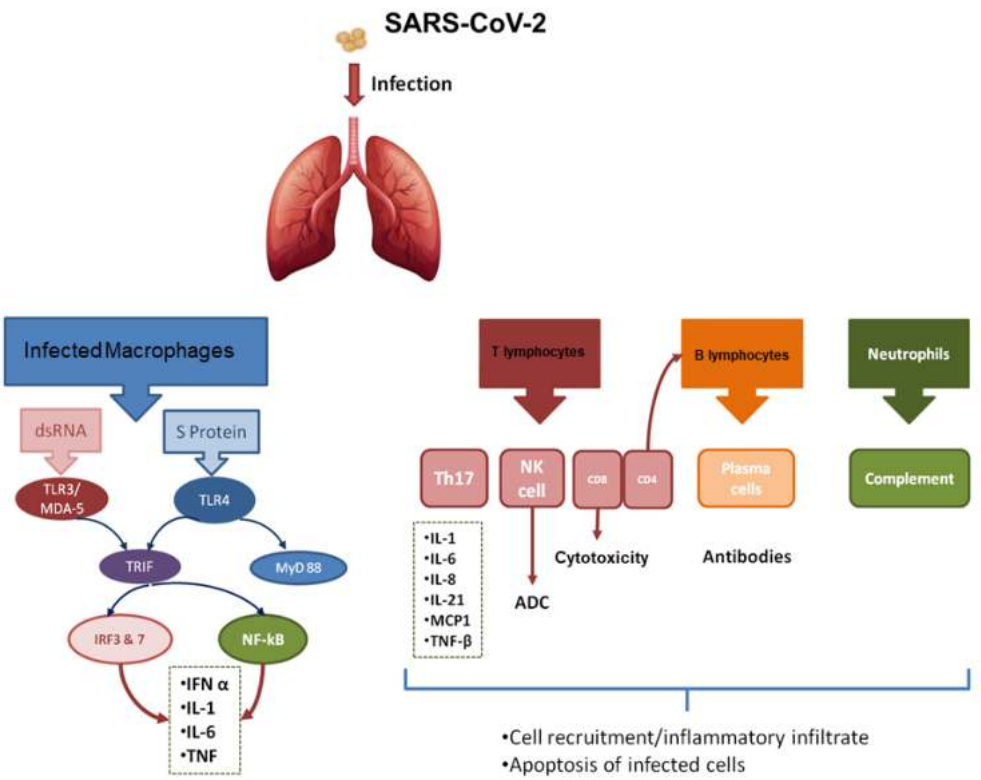
Cytokine deregulation was also thought to underlie ARDS development. Apparently, SARS--CoV2, induces abnormally low levels of antiviral cytokines, particularly type I interferons, which form part of the very early IR to viral infections (44). Such lack of an antiviral innate IR may favor a poorly controlled viral replication with progressive increases in viral load and the accompanying pro inflammatory systemic response. This situation continues until the appearance of the adaptive IR, which brings viral replication under control. Concerning SARS-CoV2, its clinical severity is related to the high viral load and the intense inflammatory response as evidenced by serum cytokine profiles and histopathology (2).

Moving to antiviral adaptative IR, CD4+ T cells, and CD8+ T cells particularly play a significant antiviral role, with the former promoting the production of virus-specific antibodies by activating T-dependent B cells; and CD8+ T cytotoxic cells, killing viral infected cells. Of note, CD8+ T cells account for about 80% of total infiltrative inflammatory cells in the lung interstitium from SARS-CoV- infected patients, being involved in coronaviruses clearance of infected cells as well as immune injury (46). Additionally, T helper cells produce pro inflammatory cytokines via the NF-kB signaling pathway. Cytokine dysregulation is of particular interest in patients with COVID-19, who have higher levels of inflammatory cytokines. However, what is more interesting is that, as seen during the SARS outbreak, some cytokines seem to be up-regulated, especially in patients with more severe disease. IL-17 cytokines recruit monocytes and neutrophils to the site of infection which in turn activate other downstream cytokine and chemokine cascades, such as IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1 (44, 46). Some studies showed that the levels of inflammatory cytokines are high in the lungs of COVID-19 patients like TNF-α and IL-1. Besides disease severity correlated with TNF-α, IL-6 and IL-10 levels (44) (Figure-4).

On the other hand, a worth considering question deals with the generation of immune memory to SARS-CoV-2. Considering the knowledge gathered from another coronaviruses, in SARS convalescents patients, memory T cell responses are directed at SARS-CoV structural proteins. These responses are found to last up to 11 years after infection. There is also evidence for an absence of cross-reactivity of these CD8+T cell responses against the MERS-CoV (46).

In summarizing, the IR induced by SARS--CoV-2 infection is two phased. During the incubation period and non-severe stages, a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to advanced

Figure 4- Diagram of the immune response to infection with SARS-CoV-2.



The intracellular response of the infected macrophage is shown on the left side of the figure. As shown, both protein S and viral RNA will induce the production of pro-inflammatory cytokines as well as type 1 interferons. The main activation pathways are those that lead to nuclear translocation of NF-kB and IRF (Interferon Response Factors). On the right side are shown the cells of the innate as well as the adaptive immune response that are involved in antiviral immunity, with the mechanisms of cytotoxicity as well as those of humoral immunity being the most relevant. TLR4, Toll Like receptor 4; MDA-5, Melanoma Differentiation Antigen 5; IFN, Type I Interferon; NK cells, Natural Killer Cells; IRF3 and 7, Interferon Response Factors; TNF-β, Tumor necrosis factor-β; MCP-1, Monocyte Chemoattractant Protein-1; Th17, T-helper 17 cells.

disease. Therefore, strategies to boost immune responses (anti-sera or pegylated IFNα) at this stage are certainly welcome. However, when a protective IR is impaired, the virus will propagate favoring a substantial destruction of affected tissues, especially in tissues that have high ACE2 expression (47). In turn, damaged cells will fuel innate-mediated inflammation in the lungs largely mediated by pro inflammatory macrophages and granulocytes. As stated, lung inflammation therefore emerges as a critical factor for life-threatening respiratory disorders at the severe stage (47).

THE DIAGNOSIS OF COVID-19 PATIENTS

Intensive testing of suspected cases to identify COVID-19 infected people is critical to avoid the further spread of infection. The *in vitro* diagnostic assays based on viral nucleic acid detection using real-time reverse transcriptase polymerase chain reaction (RT-PCR) (~80% sensitivity) remain the standard of reference (48-51) (Table-2). The assay duration has been shortened from 2-3 hours to 45 minutes; however, it is unable to detect the SARS-CoV-2 in early stages of viral infection, giving false negatives in people infected up to two weeks after symptom onset. Possible reasons for the low detection efficiency could be low patient viral load or improper clinical sampling. In this sense, chest radiography and computed tomography (CT) (~65% sensitivity) represent a complementary diagnostic tool that allows physicians to effectively make a diagnosis, reaching in many cases a higher sensitivity (~91%) by combining both tools (52).

Table 2- Summary of *in vitro* diagnostic assays based on SARS-CoV-2 viral nucleic detection

Assay type/ name	Target genes	Samples	Assay duration	Sensitivity and/or detection limit	Company/Authors
Real time RT-PCR	- Envelope protein (E) - RNA-dependent RNA polymerase (RdRp)	-Sputum -Nose and throat swabs	N.R.	-E gene: 3.2 RNA copies/reaction (95% detection) - RdRp gene: 3.7 RNA copies/reaction (95% detection)	Tib-Molbiol, Berlin, Germany, published by Corman et al. (49)
One-step real time RT-PCR	- ORF1b -N protein	-Sputum	> 1 hour	<10 RNA copies/ reaction	Published by Chu et al. (50)
Real time RT-PCR (COVID-19-RdRp/Hel assay)	-(RdRp)/ helicase (Hel) -spike (S) -nucleocapsid (N)	-Saliva -Plasma -Upper respiratory swabs	N.R.	-Hel gene: 11.2 RNA copies/reaction (95% confidence interval) -N gene: 21.3 11.2 RNA copies/reaction (95% confidence interval)	Published by Chan et al. (51)
Real-time RT-PCR rapid test (Xpert® Xpress SARS-CoV-2 test)	Two target genes (E and N2)	-Nasopharyngeal swab -Nasal wash -Aspirate specimens	45 min	0.0100 plaque forming units (PFU)/ mL	Cepheid, USA
Vivalytic COVID-19 Test (rapid test)	SARS-CoV-2 and nine other respiratory Viruses -ORF1ab -E protein	-Nose and throat swabs	< 2.5 hour	N.R.	Bosch, Germany & Randox Laboratories, UK
Abbott ID NowTM— COVID-19 test (rapid test)	-RdRp	Throat, nasal, nasopharyngeal and oropharyngeal swabs	5 min	N.R.	ABBOTT, USA

Real-time RT-PCR = real-time reverse transcriptase polymerase chain reaction; **N.R** = not reported; **UK** = United Kingdom

Other *in vitro* diagnostic assays, such as several serological immunoassays (rapid lateral flow immunoassay (LFIA) tests, automated chemiluminescence immunoassay (CLIA), and manual ELISA) detect SARS-CoV-2 viral proteins and antibodies like IgM and IgG, in the serum or plasma. The detection of IgM ranges from 10 to 30 days after SARS-CoV-2 infection; however, that of IgG from 20 days onwards (48) (Table-3).

Additionally, other routine blood examinations are used to monitor the status of COVID-19 infection, such as liver and kidney function, myocardial markers, myoglobin, ferritin, erythrocyte sedimentation rate, C-reactive protein (CRP), procalcitonin (PCT), lactate, D-dimer, complete blood count, coagulation profile, urine routine test, creatine kinase, lactate dehydrogenase, electrolytes and inflammatory factors (interleukin (IL)-6, IL-10, TNF-α). Monitoring CRP and PCT levels help to distinguish whether there was bacterial infection in the lung. D-dimer infers the risk for blood clotting (thrombosis) and/or thrombotic embolism. It has been observed that in most severe COVID-19 patients, the D--dimer level is significantly increased showing frequent clotting disorders and microthrombotic formations. Quantifying inflammatory factors, especially IL-6, may help to preliminarily evaluate the immune status of patients in terms of the cytokine release syndrome (45).

CONFLICT OF INTEREST

None declared.

Table 3 - Summary of rapid *in vitro* diagnostic serological immunoassays based on SARS-CoV-2 detection of viral proteins and antibodies.

Assay type/ name	Target proteins	Samples	Assay duration	Sensitivity and/or detection limit	Company/Authors
DZ-Lite SARS-CoV-2 CLIA*	-IgM -IgG	-Blood -Serum -EDTA plasma	~ 50 tests/hour	-Sensitivity: 90-95.6% -Specificity: 96.5%	Diazyme, USA
-2019-nCoV IgG test* -2019-nCoV IgM test*	-IgM -IgG	-Serum -Plasma	30 min	N.R.	Snibe Co, China
COVID-19 IgM/IgG Rapid Test**	-IgM -IgG	-Serum -Plasma -Blood	10-15 min	-Sensitivity: 88.66% -Specificity: 90.63%	BioMedomics, USA
SARS-CoV-2 Rapid Test**	-IgM -IgG	-Finger-pricked blood	20 min	-Specificity: 99.8 %	Pharmacyt AG, Germany
DPP COVID-19 Serological Point-of-Care Test**	-IgM -IgG	-Finger-pricked blood - Whole blood -Serum or plasma	15 min	N.R.	Chembio Diagnostics, USA

*** = automated chemiluminescence immunoassay (CLIA); ** = rapid lateral flow immunoassay (LFIA).**

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REVIEW ARTICLE

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Special strategies and management of urological diseases during the COVID-19 Pandemic: initial experiences from a Medical Center of China

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ABSTRACT

Although urological diseases are not directly related to coronavirus disease 2019 (COVID-19), urologists need to make comprehensive plans for this disease. Urological conditions such as benign prostatic hyperplasia and tumors are very common in elderly patients. This group of patients is often accompanied by underlying comorbidities or immune dysfunction. They are at higher risk of COVID-19 infection and they tend to have severe manifestations. Although fever can occur along with urological infections, it is actually one of the commonest symptoms of COVID-19; urologists must always maintain a high index of suspicion in their clinical practices. As a urological surgeon, how we can protect medical staff during surgery is a major concern. Our hospital had early adoption of a series of strict protective and control measures, and was able to avoid cross-infection and outbreak of COVID-19. This paper discusses the effective measures that can be useful when dealing with urological patients with COVID-19.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a global pandemic since the beginning of 2020. The WHO announced COVID-19 as a public health emergency (PHEIC) of international concern on January 30, 2020 (1). COVID-19 has caused many close contacts to be infected because early symptoms can be subtle; patients mainly have dry cough and fatigue, and some even present without any symptoms; this imposes substantial challenges for prevention of viral transmission (2, 3). For urology departments, both outpatient clinics and wards are high-risk areas where the virus can be exposed and spread. According to the current global case statistics, a large number

of medical staff has been infected, and some resulted in mortality. Most of the deaths caused by COVID-19 are in middle-aged and elderly patients with chronic diseases (such as tumors, cirrhosis, hypertension, coronary atherosclerotic heart disease, diabetes, and Parkinson's disease) (4). Urological conditions, such as benign prostate hyperplasia and tumors, are very common in elderly patients, who unfortunately are high-risk individuals due to underlying comorbidities and immune dysfunction (5, 6). During this critical time period of COVID-19 epidemic, we must strengthen the protection of doctors, nurses and patients in urology departments (7).

China has proactively taken strict measures to address this global pandemic at a very early stage. COVID-19 has been included as a class B infectious disease under the Law of China on the Prevention and Control of Infectious Diseases and as a class A infectious disease in terms of the planned management strategies. In the process of anti-epidemic strategy implementation, the National Health Commission of P.R. China has continuously issued and updated seven versions of the guidelines for the prevention and control of COVID-19. As of 24:00hrs on April 27, a total of 82,836 cases of COVID-19 were diagnosed in China, of which 4,633 cases died. Currently, there are 50 severe cases out of 648 confirmed cases (8). Although China's epidemic situation has not yet completely resolved, it has achieved staged victory in the control of this epidemic with substantial efforts by solid unity throughout the nation.

In this paper, we introduce the initial experiences of the special management strategies of urological diseases during the COVID-19 pandemic in China.

The prevention and control strategies of our hospital

Rearrangement of the hospital area

To prevent the potential infection risk resulting from unscreened people entering the hospital, we have set pre-examination and triage locations in front of the hospital. Qualified clinicians were arranged in rota to participate in the 24-hour work at this position to monitor the temperature of each person entering the hospital and to inquire for any upper respiratory symptoms and epidemiological history. People with a history of fever or contact with the epidemic area were mandated to receive consultation at the fever clinic.

The hospital had a strict division of personnel. There were six access channels for staff, common patients, and fever patients started at the beginning of January. Additional fever clinics and fever wards were temporarily established to cope with the sudden increase in fever patients. We also set up special equipment and channels for fever patients to receive computed tomography, ultrasound, and other auxiliary examinations.

Diagnosis and treatment items and department administration

According to the needs of epidemic prevention and control, the hospital suspended outpatient services and provided emergency dental, ophthalmological, and otolaryngological services to minimize the risk of cross-infection while the number of confirmed cases in China continued to increase. In terms of urological investigations, we suspended items such as urodynamic testing, cystoscopy, andrology examinations, and extracorporeal shock wave lithotripsy, based on the urgency of urological conditions.

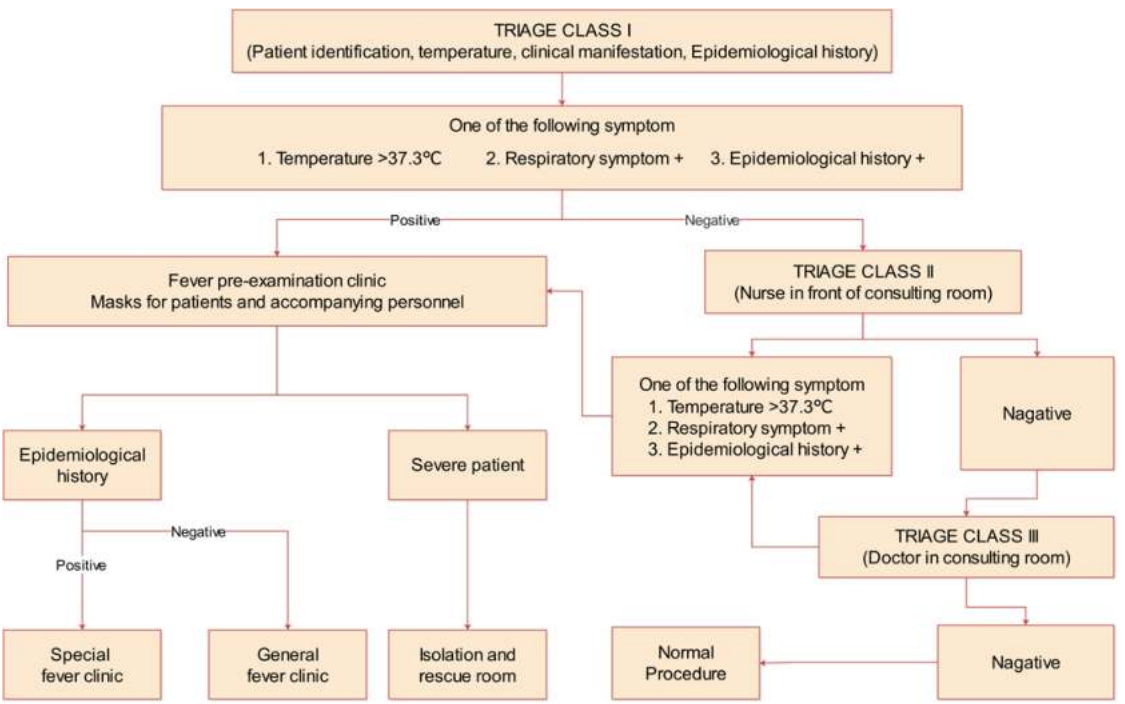
Management of the urology clinic

A three-level arrangement of pre-examination and triage was adopted for the management of the urology clinic (Figure-1). Everyone entering the outpatient building was required to wear a mask and undergo a temperature measurement. Those with body temperatures greater than 37.3°C were not allowed to enter the clinic.

1 - For medical staff

A triage nurse was required to first screen the patient for an epidemiological history and to fill out a registration form. The clinic doctor asked for the patient's medical history in detail and recorded the outpatient medical record faithfully. All medical staff needed to strengthen their awareness of hand hygiene and to strictly follow the requirements from the hospital. To avoid cross-infection, staff could not touch their faces if they did not wash or disinfect their hands. If the patient

Figure 1 - Three levels of pre-examination for urology clinic.



was suspected to have COVID-19, the "Suspicious and Confirmed Case Report Requirements and Procedures" guidelines proposed by the hospital were followed.

For patients

In addition to the examinations that required close contact, patients needed to maintain a certain distance from their accompanying family member and from the medical staff. Strict implementation of "one person, one clinic, one room" was required to avoid overcrowding in the waiting area.

Management of urology wards

There were many people in the urology ward. We adjusted the ward setting, restricted the entry and exit of patients and medical staff, and made use of the Internet technology to carry out all ward management. The specific measures were as follows:

1 - Online diagnosis and treatment: we reduced the admission of inpatients if they were non-emergencies. Urologists could participate in online consultations to answer questions for patients, which significantly relieved the pressure of the front-line medical staff. To reduce the chance of cross-infection caused by patients coming to the hospital for a consultation, urologists could also strengthen their follow-up management of discharged patients through self-developed mobile apps.

2 - Control of visitors: we restricted the number of outside visitors allowed to enter the ward. Generally, escort or visiting outside a certain time was not allowed. No more than 1 person was allowed, and no more than 15 minutes of visiting time per day per patient was allowed.

3 - Noncontact delivery: meal delivery or courier delivery from outsiders were not allowed to enter the ward. Ward control points and take-out delivery corners were set up at the entrance of the inpatient building.

4 - Ward management: all the air conditioners in the ward were turned off. Double access of passages and elevators without crossing the ward was formulated for medical staff and patients. There were 1-2 isolation cubicles in each ward. Once there was a suspected patient who needed to be quarantined on the spot, the patients

in the same cubicle were arranged for isolation to receive expert consultation and they will enter a screening process (Figure-2).

5 - The implementation of protective measures was reinforced by nurses on a daily basis: Behaviors such as poor hand hygiene, irregular use of masks, people gathering and lack of cough etiquette were corrected, followed by a thorough explanation and correct demonstration. The responsible team leader conducted two special inspections every morning and afternoon for patients and visitors/accompanying personnel.

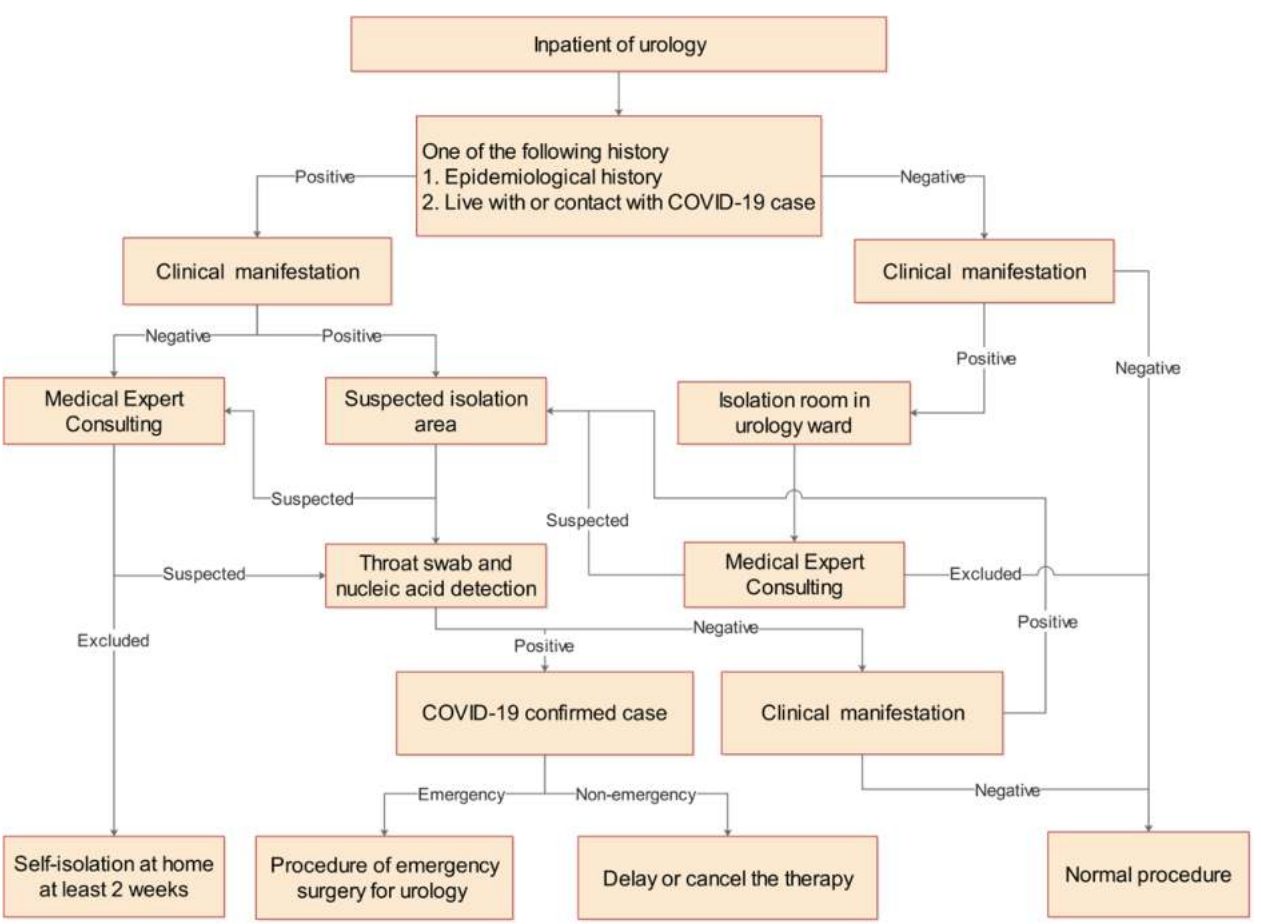
6 - All urologists were informed to stop taking vacations as well as leaving the city. Those who had not been arranged for work should rest at home. Urology staff received training to strengthen risk awareness cultivation under the requirements of the hospital. The staff was also required to participate in the relevant training exercises and pass the assessment organized by the hospital.

Treatment suggestions for urological diseases

Management of patients with fever in urology

Fever and pneumonia are common in urology patients and the differential diagnosis of COVID-19 should be considered. Patients with fever and urological symptoms, and without any respiratory symptoms, should be differentially diagnosed with urological infections. Patients with fever and respiratory symptoms should be screened according to the COVID-19 screening procedure. Moreover, necessary isolation and disinfection should be performed. In addition, any suspected cases should also be reported to the hospital infection management department and consulted by

Figure 2 - General screening procedures for patients in urology ward.



an expert group to provide assistance in diagnosis and treatment.

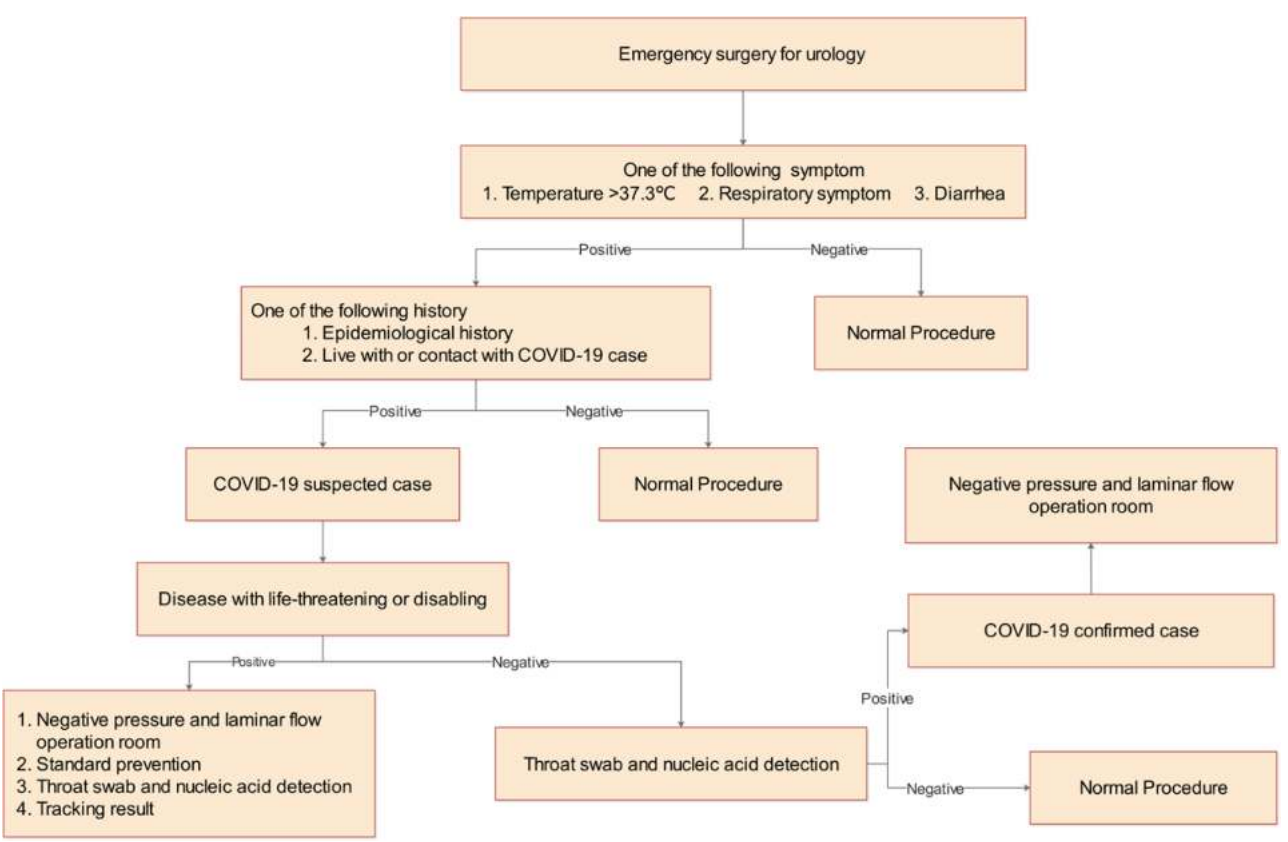
In addition, the majority of urology patients are of advanced age. CT examination of the lungs may identify asymptomatic pneumonia or febrile pneumonia. COVID-19 infection needs to be screened in these patients, and epidemiological history must be enquired to avoid the risk of asymptomatic infection. For those who are asymptomatic at the hospital but then developed symptoms during the hospitalization period, COVID-19 nucleic acid test is required and should be repeated if necessary after reporting to the hospital.

Management of patients receiving surgery

First, to avoid cross-infection, we should try to limit elective surgery as much as possible during the epidemic. Emergency or urgent surgeries should be considered under special protective circumstances. Confirmed cases should be transferred to designated hospitals for further processing. Second, when urological procedure has to be performed on suspected cases or confirmed cases, medical staff should work with protective clothing, shoes, and head coverings and should disinfect the items used by the patients, marking the designated place and time.

For patients who have life-threatening urological emergencies requiring emergency surgeries, and when COVID-19 testing results are not available, the operation needs to be performed in a negative-pressure theatre or infection operating room after consultation with an expert group. The procedure for the arrangements of emergency surgery is shown in Figure-3. The patient should enter the operating room with a mask. The medical staff should adopt level three protection with surgical gowns and shoe covers, protective clothing, goggles or face screens, and N95 masks (European mask standard EN149: 2001 (FFP2). At the same

Figure 3 - Procedure for emergency surgery of urology during COVID-19 pandemic.



time, minimal use of items and restriction of medical personnel should be considered. After the operation, the protective equipment must be removed in order. The in-time cleaning and disinfection of the operating room is necessary. If the patient is diagnosed with COVID-19 after surgery, a detailed report to the medical administration department and self-monitoring with isolation for 2 weeks for the participating surgical staff are required.

Collection of stool specimens

Stool specimens are commonly collected for various laboratory investigations. Due to the existing evidence that COVID-19 viral RNA can be detected in stool, the stool samples should be carefully handled during the collection and submission period (9, 10). Viral RNA has also been detected in urine samples, but the rate is very low. Any leakage or cross-infection can be avoided by stringent procedures.

The preparation before stool collection for patients with confirmed or suspected COVID-19 should include a closed sterile container with stool, a closed bag for all patients and a disposable urine cup if probable for female patients. The collected stool should be placed in a sterile, closed container. The samples must be marked for patients with COVID-19 and must indicate the patient's information that needs to be collected. Leaving the stool outside the container is forbidden during the collection process. If this really happens, immediate wiping with a sterile towel and ethanol more than 5 times before putting the sample in a closed bag are required. The samples should be stored at 4 degrees centigrade if long-distance transshipment is needed. The sample should be kept at 4 degrees centigrade if the detection time is within 5 days; otherwise, 70 degrees below centigrade is required. To reduce the possibility of exposure to pathogens, all samples collected for laboratory testing should be considered potentially infectious. Health care workers collecting and transporting clinical samples should strictly abide the guidelines for infection prevention and control. In addition, proper communication should be carried out to ensure proper specimen collection and to guarantee the lowest possible risk of infection to the collector.

CONCLUSIONS

"Prevention is better than cure" – it is the golden rule for any infectious disease at any time. The patients seen by urologists are mostly elderly people, who are the frequent population suffering from severe diseases. We must strengthen protection and health education in order to fight against this disease.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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COVID-19's Impact on Italian Urology

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ABSTRACT

The COVID-19 pandemic has impacted our lives, our habits and our healthcare system. Italy is one of the countries affected first and more aggressively from the outbreak. Our rapidity has been guide for other healthcare systems from around the World. We describe the impact of COVID-19 on Urology, how the Urological scientific community responded to the emergency and our experience in a high-volume Roman University hospital. The aim of our work is to share our experience providing suggestions for other global hospitals on how to manage the COVID-19 emergency.

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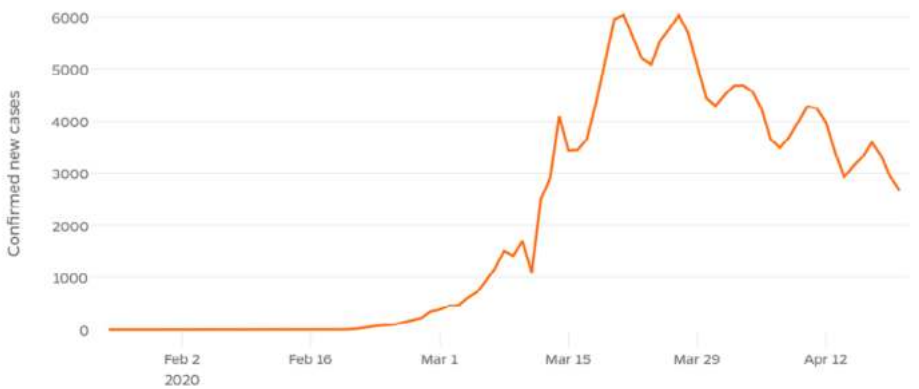
EPIDEMIOLOGY

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, Hubei Province, China, in December 2019 (1). The disease has been termed COVID-19 and on March 11th 2020, The World Health Organization (WHO) declared it as a pandemic (2). On April 21st, 2,585,468 COVID-19 positive cases and 178,854 deaths have been confirmed worldwide. The United States, Spain and Italy were the most affected countries with 825,306, 208,389 and 183,957 positive cases respectively (3).

ITALY

COVID-19 was first detected in Italy on January 30th, and the Italian government immediately declared the state of emergency. A COVID-19 task Force and a Special Commissioner for the Emergency were appointed. On February 23th, a ban was put on entry and exit in the municipalities where outbreaks occurred, and public events were suspended. National lock down was officially announced on March 9th (4). The number of cases increased since the first case and peaked in mid-March (Figure-1) (5).

Figure 1 - The outbreak evolution curve of confirmed COVID-19 new cases in Italy from Feb 2 to April 12 (5).



On April 29th the number of COVID-19 associated deaths was 26,977. A total of 17,997 healthcare workers were tested positive for COVID-19 (median age 48 years, 32% male), which accounted for 10.7% of the total number of reported cases. The high transmission potential of the virus in the healthcare sector was evident (Figure-2) (6). Overall, 79,370 cases were male (50.0%) and the median age amongst both genders was 62 years (range 0-100). In the age groups 0-9, 10-19, 60-69 and 70-79 years, a greater number of male cases compared with female were observed. There was an increase in lethality with increasing age of cases. Lethality was higher in male subjects in all age groups, except for the age group >90 years. In 31.1% of the reported cases, at least one co-morbidity was identified (cardiovascular, respiratory, diabetes, immune deficiencies, metabolic, oncological, obesity, kidney and other chronic pathologies) (6). Presenting symptoms of COVID-19 patients included fever (75%), dyspnea (72%), cough (38%), diarrhea (6%), hemoptysis (1%). Overall, 60.7% of COVID-19 deaths were associated with 3 or more pre-existing diseases (4). The distribution of COVID-19 cases varies within the country. The north is much more affected and is reflected on the mortality rate (Figure-3) (3).

At the 28th of April the most affected regions were Lombardy, Piedmont, Emilia-Romagna, Veneto, Tuscany and Liguria with an amount of total cases detected of 74348, 25450, 24914, 17708, 9231, 7772 respectively. The mortality rate was the following: 18.3 % in Lombardy, 11.5 % in Piedmont, 13.9 % in Emilia Romagna, 7.95 % in Veneto, 8.8 % in Tuscany, 14.7 % in Liguria.

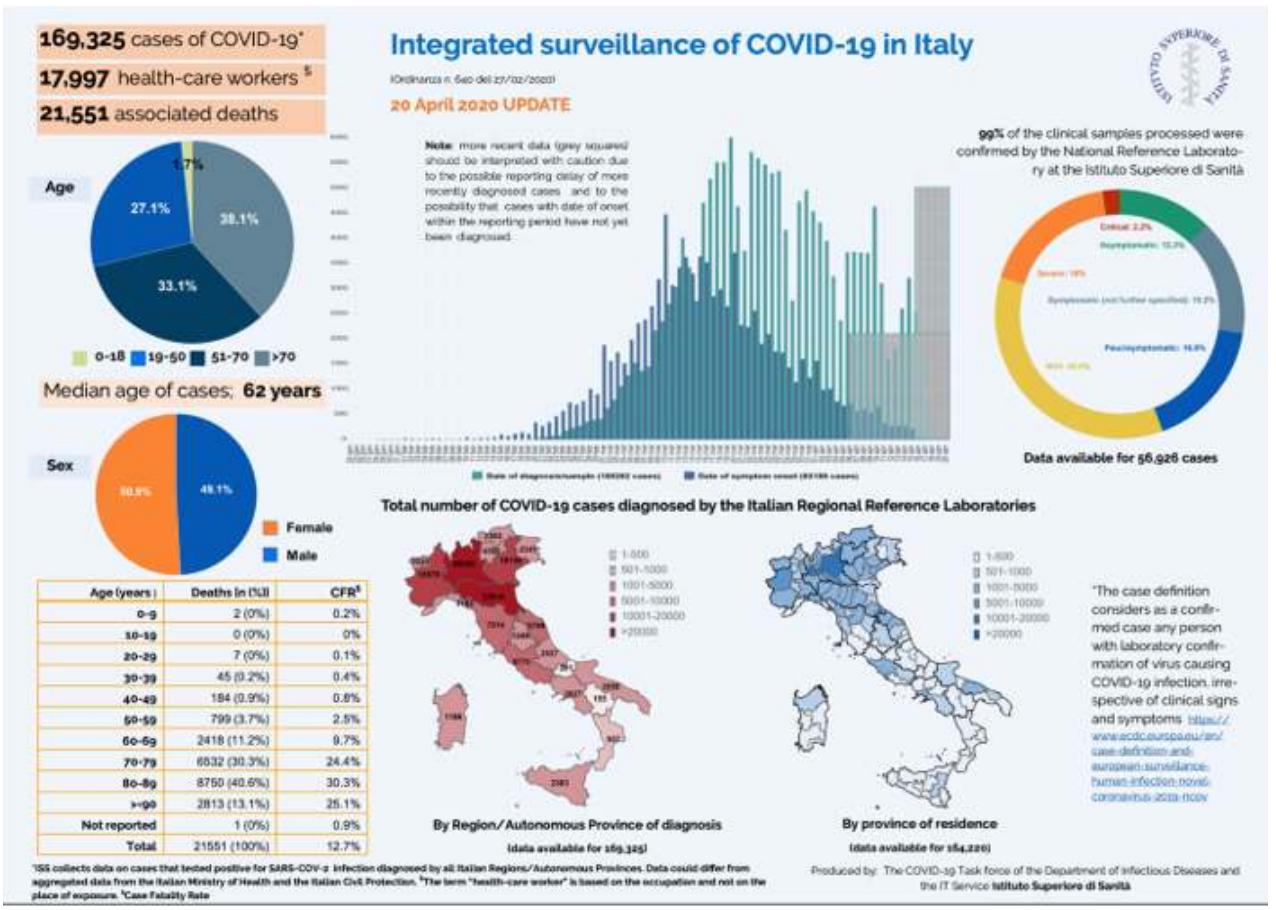
The less affected regions were Calabria, Basilicata and Molise with a mortality rate of 7.7 %, 6.8 %, 7.1 % respectively. Lazio with 6467 cases detected had a mortality rate of 6.4 %.

Intensive care units (ICUs) filled up quickly with COVID-19 patients and became stretched to accommodate non-COVID-19 patients who required critical care. In Lombardy Grasselli et al. described a mortality rate of 26% in ICUs as of March 25, 2020 (7). The initial lack of personal protective equipment (PPE) and swab testing led to a rapid spread. Healthcare professionals were being infected, reducing the number of healthcare workers (HWs) available to manage the emergency. However, the situation was different in less affected regions where there was more time to prepare and organize resources and HWs to manage the pandemic.

MEASURES

Members of the RUN (Research Urology Network) group provided guidance on the management of urological patients during the COVID-19 era. They suggested treatment for urgent or emergent urological conditions only. Factors affecting the categorization of procedures included the need for postoperative intensive care, need for blood transfusion or

Figure 2 - Integrated surveillance of COVID-19 in Italy (6).



Age (years)	Deaths (n (%))	CFR§
0-9	2 (0%)	0.2%
10-19	0 (0%)	0%
20-29	7 (0%)	0.1%
30-39	45 (0.2%)	0.4%
40-49	184 (0.9%)	0.8%
50-59	799 (3.7%)	2.5%
60-69	2418 (11.2%)	9.7%
70-79	6532 (30.3%)	24.4%
80-89	8750 (40.6%)	30.3%
>=90	2813 (13.1%)	25.1%
Not reported	1 (0%)	0.9%
Total	21551 (100%)	12.7%

*ISS collects data on cases that tested positive for SARS-COV-2 infection diagnosed by all Italian Regions/Autonomous Provinces. Data could differ from aggregated data from the Italian Ministry of Health and the Italian Civil Protection. §The term "health-care worker" is based on the occupation and not on the place of exposure. §Case Fatality Rate

other blood products, cardiovascular, respiratory or infective comorbidities, and the need for psychophysical support. Indications in postponing up to six months prostate biopsies, flexible cystoscopies, replacements of ureteral stents and nephrostomy tubes, intravesical therapy for low and intermediate risk bladder cancers have been provided (Table-1) (8).

The admission pathway included pre-admission telephone triage, nasopharyngeal swabs, PPE, strict rules in the operating room (9). Ribal et al. produced dedicated European Associations of Urology (EAU) guidelines on the management of Urological patients during the COVID-19 outbreak (10). Despite strong efforts in trying to prioritize oncological and urgent procedures, the burden of oncological patients on waiting list is increasing. Campi et al. described the progressive reduction in all elective's procedures in three high volume Urology centers in Italy (11).

Impact on training

Resident's programs in Europe and in Italy are just harassed from a lack of adequate academic and surgical training (12-15) and it is known how its associated frustration may lead to burnout (16). Several papers described a global slowdown of Urology residence program during the pandemic (17-19). Social Media and smart learning implementation have been proposed as valid tools to supply scientific knowledge during this scenario (20, 21). Our group asked 'what should be the role of residents during a pandemic?'. On calling the Hippocrates statement (Afhprism 1,1) "Ὁ βίος βραχύς, ἡ δὲ τέχνη μακρή, ὁ δὲ καιρὸς ὀξύς, ἡ δὲ

Figure 3 - Distribution of COVID-19 cases in Italy (3).

πεῖρα σφαλερή, ἡ δὲ κρίσις χαλεπή" "Vita brevis, ars longa, occasion praeceps, experimentum periculosum, iudicium difficile", we think residents should play an active role alongside the specialist by exploiting the pandemic as an unrepeatable opportunity from which to learn upon (22). In general, the COVID-19 emergency is a highly dynamic situation and the burden on the healthcare system varies daily according to the geographical region.

Our Experience

Campus Bio-Medico University is a high--volume university Hospital in Rome. It has no Accident and Emergency (A and E) Department and currently is COVID-19 free. We continue to operate on oncological and urgent patients with safety precautions. Information about the virus, local policies, patients' access to the hospital, surgery protocols and individual protection have been provided to all HWs (Table-2). Every 8 hours a FFP2 mask is made available at the main entrance of the hospital. An open Outpatient COVID-19 Clinic (composed of 2 senior and 3 junior Internal Medicine Consultants) for HWs has been established to review those with symptoms or have been in close contact with a positive or suspect COVID-19 patient.

Access to the Hospital is regulated through telephone triage to rule out any symptoms or suspicion of COVID-19. In suspected cases, responsible physicians would call to clarify. In non-suspected cases, patients could go for hospital admission as pre-planned. In suspected cases, patients are instructed to stay at home and call their GP for further advice. The access to the hospital is allowed from a unique entrance with security check.

A surgical facemask and hand hygiene with 60% alcoholic solution are provided to everyone at the entrance. Temperature is checked through a thermoscanner, symptoms are checked and reason for admission is evaluated. If no issues are encountered during this phase, patient can ac-

Table 1 - Factors potentially affecting the choice of the different urological procedures during COVID- 19 pandemic (8).

Procedure	Indication for the emergency phase	Note
Prostate biopsy	Postpone	Reconsider performing prostate biopsy in patients with high clinical suspicion of prostate cancer if the emergency phase should prolong
Flexible cystoscopy	Postpone	Reconsider performing cystoscopy in patients with high risk bladder cancer if the emergency phase should prolong
Replacement of ureteral stents and nephrostomy tube	Postpone up to 6 months	
Intravesical therapy for high risk bladder cancer	Do not postpone	
Intravesical therapy for low or intermediate risk bladder cancer	Postpone	

cess the hospital. If any doubts are raised during the admission check, the responsible physician would review the case and decide whether to proceed with pre-planned admission or to refer to a dedicated COVID team.

We have detected three positive patients (in droplet isolation inside the hospital from the beginning of their admission) who have been transferred to COVID-19 centers within 48 hours. All the healthcare staff who had been in contact with them have been swabbed twice with negative results, showing the efficacy of the policy undertaken.

Visitors are allowed to access the hospital for a limited span of time (1 hour) and only one person per patient are allowed to visit after strict security checks performed at the main entrance.

We developed telemedicine protocols for outpatient's clinic and arranged virtual multidisciplinary meetings for oncological patients. Our surgical activity increased in volume, performing exclusively elective oncological and urgent operations. All patients treated have been called two weeks after discharge and none have declared any symptoms of COVID-19.

CONCLUSION

COVID-19 emergency is a highly dynamic situation and the burden on the healthcare system varies daily according to the geographical region. Through meticulous hospital instructions, prompt adoption of PPE, controlled access to the hospital, and prompt management of suspected/positive cases, we were able to maintain a COVID-19 free hospital and to continue our surgical activities during the pandemic.

Table 2 - Summary of the COVID-19 task force actions regarding PPE of Health workers (HWs).

Front office staff working		Healthcare personnel in contact with patients					Laboratory staff in contact with biological samples
At station in direct contact with patients	At station with protective glass	In contact with a suspected or confirmed case of COVID-19	In contact with a patient who presents symptoms of fever and / or cold and / or cough	Performing endoscopic procedures	Assigned to take a biological sample for COVID-19 + patient	Anesthesiologists performing intubation	
frequent hand hygiene by using 60 % alcohol solution	frequent hand hygiene by using 60 % alcohol solution	FFP2 filtering mask (use FFP3 only for the procedures that generate aerosols)	FFP2 filtering mask (use FFP3 only for the procedures that generate aerosols)	FFP3 filtering masks	FFP3 filtering mask	FFP3 filtering mask	FFP3 filtering mask
wear the FFP2 filtering mask during the entire work shift	/	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes
wear protective glasses from liquids splashes during the entire work shift	/	water repellent PPE coat	/	water repellent PPE coat	water repellent PPE coat	water repellent PPE coat	water repellent PPE coat
provide a surgical mask, supplied at the desk, to be worn by the patient with visible respiratory symptoms	provide a surgical mask, supplied at the desk, to be worn by the patient with visible respiratory symptoms	double gloves	gloves	gloves	double gloves	double gloves	double gloves

CONFLICT OF INTEREST

None declared.

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Endourology and Benign Prostatic Hyperplasia in COVID-19 Pandemic

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ABSTRACT

The new disease COVID-19 pandemic has completely modified our lifestyle, changing our personal habits and daily activities and strongly our professional activity.

Following World Health Organization (WHO) and health care authorities around the World recommendations, all elective surgeries from benign diagnose procedures must be postponed and imperatively continue working on emergent and oncological urgent pathologies. Surgical elective treatment of benign prostatic hyperplasia (BPH) is not considered as a priority.

During BPH endoscopic surgeries, urine and blood are mixed with the irrigation liquid implying a risk of viral presence. Furthermore, a steam and smoke bubble is being accumulated inside the bladder implying the risk of splashing and aerosols. The risks of other viral infections have been identified during endourological procedures and they are related to splashing events. Several studies observed 33-100% of splashing on goggles.

All BPH endoscopic procedures must be postponed. In case of complete urinary obstruction, this event can be adequately treated by urethral or suprapubic catheter under local anesthesia.

As soon as local COVID-19 prevalence decreases, endourological procedures could be restarted. As protocols are being validating around the World to redeem elective surgeries, a symptomatic obstructed patient could be operated knowing his COVID-19 status with a molecular PCR, a cleaned epidemiological interview with a normal preoperative protocol.

If patient is COVID-19+, surgery must be delayed until complete recovery, because mortality could increase as Lei from Wuhan describes.

Informed consent must include risks of complications related to COVID-19 disease.

Surgery must be performed by an experienced surgeon in order to avoid increase of operating time and risks of complications.

Surgical approach of BPH must be considered depending on availability of disposable material, infrastructure, and the epidemiological COVID-19 status of your area. The main aim is patients and healthcare staff safety.

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INTRODUCTION

The coronavirus named SARS-CoV-2 is causing an outbreak of a new disease COVID-19. This pandemic has completely modified our lifestyle, changing our personal habits and daily activities and strongly our professional activity. At this point, current medical data and its clinical applications as suggested by conventional guidelines has had to be adapted to the feasibility of this new state of affairs.

Nowadays, we face a new disease on Earth and there are not high level of evidence recommendations to deal with. Furthermore, during this pandemic, we have to follow expert recommendations modifying our urological indications and out-patient and in-patient schedules prioritizing emergent and urgent procedures in order to avoid a life-threatening situations or disease progression and/or maintain patient and sanitary staff safety with novels biosecurity protocols.

Following World Health Organization (WHO) and health care authorities around the World recommendations, all elective surgeries from benign diagnose procedures must be postponed and imperatively continue working on emergent and oncological urgent pathologies. Unfortunately, in this context, surgical elective treatment of benign prostatic hyperplasia (BPH) is not considered as a priority.

However, this is a dynamic situation and information is evolving rapidly, so it is important to consider the status of your institution and locality to continue or recover your usual practice as proposed by the American College of Surgeons (1).

Risks during endourological procedures:

SARS-CoV-2 is a RNA virus belonging to the beta coronavirus family able to infect the upper respiratory tract. Spread mechanisms have been studied and identified from human-to-human respiratory interactions to airborne and fomites transmissions (2-8).

In a hospital setting, knowing the extent of environmental contamination of SARS-CoV-2 in hospital wards (HW), operating room (OR) and intensive care units (ICU) is critical for improving safety practices for sanitary staff. Airborne and touching-fomites transmission have been observed in COVID dedicated ICUs and HWs (6).

Some specific aerosol-producing procedures as endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation, are considered high-risk situations (4,6). Furthermore, all aerosolization procedures are a security key point to be considered.

Carcinogenetic hazard and risk of transmission of several bacteria and virus as *corynebacterium*, tuberculosis, human immunodeficiency virus (HIV), human papillomavirus (HPV) and Hepatitis B have been described in different studies related to surgical smoke (9-13). At that point, many questions have been posed about biosecurity in open, endoscopic and laparoscopic / robot assisted surgeries (13-15).

Some risks during endourological procedures have been identified and they are related to splashing events and smoke/aerosolization producing procedures. SARS-CoV-2 RNA has been found also in blood, feces and urine implying a potential risk of transmission during endoscopic surgeries (16-21).

All surgeons are aware of risks of viral transmission in blood splashing, however they are underestimated. Those who use routinely goggles notice these droplets over them. Several studies observed 33-100% of splashing on goggles (22-24) as shown in Table-1. Moreover, not only on the chief surgeons but in assistants too, so eye protection is strongly suggested in each endourological procedure (24).

In relation to aerosolization and smoke produced, the hazard in endoscopic procedures are moderate compared with the biological and carcinogenetic risks observed in open and laparoscopic surgeries (13). Laparoscopic procedures are related with high concentrations of surgical smoke and 10 times aerosol potential exposure (15) but at the same time they are a natural physical barrier, this aerosolization hazard has the opportunity of being very well controlled. Current ablative BPH

Table 1 - Splashing blood events on eye protection.

Author	Procedure	What was examined	Splash event
Davies and Harrison (22)	Transuretral Resection	Blood on Spectacles	100%
Muir and Davies (23)	Video Resection	Blood droplets on goggles	66%
Wines et al. (24)	Video TUR	Blood droplets on goggles	33%
Wines et al. (24)	Flexible URS	Blood droplets on eyes shield	58%

endoscopic technologies deliver thermal energy to cut, resect, vaporize and coagulate prostatic tissue. These well-known technologies use electrical (monopolar and bipolar) and laser (holmium, thulium, KTP, diode) sources of energy allowing a huge variety of procedures including transurethral resection, plasma bipolar and laser vaporization, and laser enucleation. During these surgeries, urine and blood are mixed with the irrigation liquid implying a risk of viral presence. Furthermore, a steam and smoke bubble are being accumulated inside the bladder implying the risk of splashing and aerosols even if no COVID-19 transmission has not been reported by this way.

COVID-19 and Benign Prostatic Hyperplasia (BPH)

Since hospitals will face a huge demand of resources to fight against a possible surge of COVID-19 cases, elective surgeries of benign pathology have been recommended to be delayed until the strain on the hospital system from COVID-19 decreases. Following this rules, all BPH procedures as TURP, HoLEP, ThuLEP, PVP, etc. must be postponed. In case of complete urinary obstruction, this event can be adequately treated by urethral or suprapubic catheter under local anesthesia (25, 26).

As soon as local COVID-19 prevalence decreases (26), endourological procedures could be restarted. As protocols are being validating around the World to redeem elective surgeries, a symptomatic obstructed patient could be operated knowing his COVID-19 status with a molecular PCR, a cleaned epidemiological interview with a normal preoperative protocol. If patient is COVID-19+, surgery must be delayed until complete recovery. Informed consent must include risks of complications related to COVID-19 disease. Ti et al. reported up to 20% mortality rate in asymptomatic COVID-19+ patients which were unintentionally programed for elective surgery (27).

Including non COVID-19, all patients must be considered as suspected ones. At this point, surgical staff including scrub nurse and anesthesiologist must wear a level 2 or 3 PPE. Initially, only the anesthesiologist and the assistant must be inside the OR with the patient. Once the patient is anesthetized, surgical staff can enter into the OR. It is important to minimize the number of strictly needed people and to count with all required materials in order to avoid frequent door openings (28). Surgery must be performed by an experienced surgeon in order to avoid increase of operating time and risks of complications. During surgery, in order to minimize smoke or aerosol risks, surgeon must be attentive to exchanges of equipment, to systematically aspirate the gas bubble and the outflow drainage connected to the central aspiration system.

CONCLUSIONS

Endoscopic procedures apparently are not as hazardous as open or laparoscopic approaches because aerosolization and smoke carcinogenetic risks and viral transmission are less frequent.

Surgical approach of BPH must be considered depending on availability of disposable material, infrastructure, and the epidemiological COVID-19 status of your area. The main aim is patients and healthcare staff safety.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Endourology (Lithiasis). Management, surgical considerations and follow-up of patients in the COVID-19 era

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ABSTRACT

Purpose: To provide recommendations on the endourological management of lithiasis in the scenario of the COVID-19 pandemic.
Materials and Methods: A non-systematic review in PubMed and the grey literature, as well as recommendations by a panel of stakeholders was made, regarding management, surgical considerations and follow-up of patients affected by lithiasis in the COVID-19 era.
Results: Under the current outbreak and COVID-19 pandemic scenario, patients affected by lithiasis should be prioritized into low, intermediate and high risk categories, to decide their delay and save resources, healthcare personnel, beds and ventilators. However, patients with potentially serious septic complications need emergency interventions. The possibility of performing or restarting elective activity depends on local conditions, the availability of beds and ventilators, and the implementation of screening protocols in the context of the COVID-19 pandemic. Delaying lithiasis surgery and increasing waiting lists will have consequences and will require considerable additional effort. Teleconsultation may be useful in guiding these patients, reducing visits and unnecessary exposure.
Conclusions: categorization and prioritization of patients affected by lithiasis is crucial for management, surgical selection and follow-up. Protocols, measures and additional efforts should be carried out in the current situation of the COVID-19 pandemic.

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INTRODUCTION

The appearance of COVID-19 has dramatically influenced our lives, as well as medicine and urology practices. The epidemic began in December 2019 in China, to spread voraciously worldwide and become a pandemic early 2020.

The reality and policies are different

among regions and countries. During the outbreak, all health efforts and resources are addressed to COVID-19 patients and to contain the contagion. Recommendations were made to prioritize surgeries, basically to postpone and reschedule non-urgent procedures to avoid unnecessary visits and spare resources, including health professionals, beds and ventilators(1-3).

Lithiasis management includes a wide spectrum from asymptomatic patients to patients requiring a non-delayable intervention, (e.g. lumbar pain and fever due to obstructive lithiasis). There is a lack of consistent evidence regard lithiasis management in the current COVID-19 pandemic scenario. Safety and feasibility of elective lithiasis surgery is variable and uncertain, depending on local conditions as well as availability of resources. The impact on the activity of urology departments and clinical practice is clear and delay in treatment may bring consequences(4, 5). Moreover, the implementation of protocols to adapt to the "new normal" requires additional efforts.

We understand the heterogeneity and asymmetry of the pandemic among the countries under CAU umbrella. We only express the opinion and recommendations of a panel of stakeholders, based on the available literature and clinical experience in attempt to achieve the best possible practices on lithiasis management, in a highly changing scenario that may not represent the reality on all countries and regions; requiring adaptation with the best clinical sense, based on the evolution of evidence and local conditions.

We aim to provide recommendations on the endourological management of lithiasis in the scenario of the COVID-19 pandemic.

Visits and diagnosis

The COVID-19 pandemic situation is exceptional and generates enormous pressure on health systems. A drastic change from face-to-face visits to telemedicine occurred in urology as well as in other specialties(6, 7). Depending on local regulations, telemedicine is a feasible option to triage patients, offering the advantages of reducing unnecessary hospital physical visits and the risk of transmission(3,8). Counseling for asymptomatic patients, preoperative or post-operative guidance can be performed by teleconference. Medical expulsive therapy (MET) may be offered to patients with uncomplicated renal colic due to ureteral lithiasis. However, obviously a main limitation of teleconferences is to conduct a properly physical examination.

Ancillary test, like ultrasound, X-ray, lab analysis or CT scan could be addressed, but may be limited and should be requested in a rationale way under the current situation of the outbreak. Face-to-face visits are expected to increase again as the incidence drops and patients feel safe. However, telemedicine may continue to be implemented after the outbreak.

Keep patients and urology team safe. For face-to-face, it is not necessary to test all patients attending, but it is highly recommended that suspicious symptoms (fever, cough, headache, muscle pain, diarrhea, conjunctivitis, anosmia, or loss of taste) and contact with COVID-19 patients should be asked by phone before (3). Apply measures including a physical distance of 2 meters, frequent hands washing, longer time between patients and limit waiting room occupancy is recommended. Patients should wear mask and gloves and health professionals properly personal protective equipment (PPE) based on recommendations (Table-1), including masks (preferably FPP3), shield and gloves (3).

Indications and prioritization of surgeries

With the determination to postpone all elective surgical procedures in most affected countries by the COVID-19 pandemic, the term "elective" is open to different interpretations. Elective procedures can be stratified as "essential", which implies that there is an increased risk of adverse outcomes when delaying surgical care for an indefinite period of time, compared to "non-essential", which alludes to purely elective procedures that are not time sensitive for medical reasons (9).

In this scenario, urologists around the World will have to choose which surgeries should be maintained in the current circumstances (2). It is necessary to discuss the topic in order to minimize the impact and risks for patients and health professionals who provide urological care. Indica-

Table 1. Personal Protective Equipment (PPE) recommended for health professionals, in contact with patients during covid-19 outbreak.

	Front office staff working	At face to face visit	Performing endoscopic procedures	Anestesiologist performing intubation	Assigned to take biological samples from COVID-19 patient or laboratory personnel in contact with samples	In contact with suspected or confirmed case of COVID-19	In contact with symptomatic patient (cold, cough, fever)
Physical distance of > 1.5 mt if possible	+++	+++	-	-	-	+++	+++
Patient should wear a mask / provide a mask to the patient	+++	+++	+++	+++	+++	+++	+++
Wear ffp2 mask	+++	+++	+++	+++	+++	+++	+++
Wear ffp3 mask	+	++	+++	+++	+++	+++	+++
Frequent hand hygiene, washing or by using 60% alcohol solution	+++	+++	+++	+++	+++	+++	+++
Wear Gloves	+++	+++	+++	+++	+++	+++	+++
Wear Double gloves	+	+	++	++	+++	+++	+++
Wear goggles, shield or barrier to protect eyes from biological liquids splashes	++	++	+++	+++	+++	+++	+++
Water repellent coat	+	++	+++	+++	+++	+++	+++

highly recommended/mandatory = +++, medium recommended = ++ , weak recommended/optional = +

tions and prioritization of lithiasis surgery during COVID-19 outbreak are summarized in Table-2.

According to the American College of Surgeons (10) to assess the real impact of the pandemic on elective procedures, it is important to understand the availability of resources at local facilities, such as: number of beds, tests, operating rooms, as well as their restrictions, such as workforce, supply chain, etc. In addition, the cancellation of surgeries contributes to social isolation and saves resources such as personal protective equipment (PPE) for the care of patients with COVID-19 infection.

Numerous patients with confirmed or suspected COVID-19 will require urgent surgical treatment (11). All postponable procedures must be rescheduled in order to reduce the exposure of the surgical team and the patient to potential contamination (4). A delay in procedures after the end of the COVID-19 pandemic is inevitable, and hospitals must plan how to deal with it effectively, ensuring that patients who has elective treatment presents the best possible results (12). Undoubtedly, the consequences of reckless elective surgery cancellations can have a more dramatic and immeasurable impact on the health of our communities than the morbidity and mortality inflicted by the new disease caused by the new coronavirus (9).

Some actions must be taken in order to reduce the spread of the disease during surgery, such as: using as much disposable material as possible, keeping the operating room doors closed, except for the circulation of employees, patients and instruments. Never handle instruments without gloves, avoid using cutting materials when possible (11). To define the indications for endourological procedures, it is necessary to proceed with the same care. Published studies on the detection of SARS-CoV-2 in urine are inconclusive and the

Table 2. Indications and Prioritization of lithiasis surgery during COVID-19 outbreak.

TREATMENT				
Priority Category	Low	Intermmediate	High	Emergency
	Up to 6 months	4 to 12 weeks	2 to 4 weeks	Up to 24 hours
COVID - RECOMMENDATIONS				
Drainage- JJ Catheter or Nephrostomy				1) Obstructive ureteral stone with infection 2) Sepsis due to obstructive stone, anuria 3) Post-operative complications (abscess, fistula, avulsion)
Urgent descompression (JJ Catheter or Nephrostomy) or endourological stone removal			1) Obstructive ureteral stone failed MET (> 4 weeks) or too large to pass (e.g. > 08-10mm) 2) Symptomatic ureteral stone, not controlled with medication, or recorrent ED visits 3) Obstructive ureteral stone with AKI 4) Recorrent infections in obstructive ureteral stone despite drainage and antibiotics 5) Staghorn stones with uncontrolled infection 6)Patients with nephrostomy (obstructive stone) or PCNL 2nd time	1) Obstructive ureteral or pyelic stone in solitary kidney, bilateral ureteral obstruction and intractabal symptoms requiring admission
Treatment - endourological stone removal		1) Ureteral stone, symptoms controlled, undergoing trial of MET 2) Ureteral stone with pre-existing stent with stent associated symptoms requiring medications 3) Recurent infections in non obstructive renal stones requiring antibiotics and with worsen renal function 4) Renal stones causing intermitent obstruction		
MET		1) Asymptomatic non-obstructive ureteral stone		
Interventional treatment (SWL, URS F-URS and PCNL)	1) Asymptomatic / oligoasymptomatic renal stones (without UTI and worsen of the renal function) 2) Majority of the stones requiring PCNL and F-URS			
JJ Catheter removal (endourological intervention when necessary)	1) Patients with JJ catheter with periodic changes	1) Patients with JJ catheter requiring definitive treatment 2) Ureteral or renal stone with pre-existing stent with well tolerated symptoms		1) Patients with JJ catheter requiring hospitalization (pain, infection and severe haemathuria)

Observations:
Stone treatment is preferred over drainage to diminish the ED visits
SWL has lower stone free rate and higher rate of secundary stone treatment, so URS is preferred
Always consider the risk group in order to indicate the surgery (immunocompromise, diabetes, renal dysfunction)
Consider stenless or stent-on-string to avoid clinic visit when possible

evidences are not yet robust. Only one Chinese study reported the presence of viral RNA in urine samples of approximately 6.9% of infected patients (13).

In the last decades, elective and emergency admissions related to urolithiasis have increased (14). Uro-sepsis due to untreated obstructive pyelonephritis or a calculus matrix with bacterial colonization are more frequent than in the past (15). Urolithiasis patients scheduled for surgery should be carefully selected according to surgical priority. Although urinary lithiasic disease represents a benign condition, in a significant number of cases it can lead to potential serious septic complications that could increase the burden on emergency services (1). Therefore, it is recommended that endoscopic procedures and urethral catheterization be performed with caution and surgeons be fully protected against infections if the patient is suspected or confirmed COVID-19 (3).

Fever can be a confusing factor in the surgical indication of patients with urinary tract obstruction, since this symptom may be due to COVID-19 and not due to bacterial infection (16). It is worth mentioning that, even with the decompression of the urinary system, antibiotic therapy and other supportive actions, 15% of these patients with sepsis require admission to the intensive care unities (ICU), with a mortality rate of 8 to 10% (15).

Therefore, most urolithiasis surgical treatments should be suspended, unless they are emergency surgeries, as in the case of obstructive pyelonephritis. In this case, one must choose to drain the urinary tract with a double J catheter implant under spinal or even local anesthetic block. Percutaneous nephrostomy can be considered when indicated (local anesthesia). Cases of ureteral obstruction in a single kidney, bilateral ureteral obstruction, acute impairment of renal function and refractory pain to clinical treatment should not be delayed. The remainder of cases of acute flank pain should preferably be treated clinically with medical expulsive therapy (MET) (4).

In situations when ureteral catheters are needed, the use of double J with external wire should be considered, to reduce the need for an additional procedure to remove it. In many cases, the patient would be able to remove the stent at home, avoiding a new visit to the hospital (13). Patients with indwelling catheter prior to the COVID era, without symptoms or oligosymptomatic, may stay with the catheter longer if necessary; on the other hand, for cases operated during the pandemic, we should try to remove a double J catheter as soon as possible, on an outpatient basis with local anesthesia, without the need for hospitalization (17).

The ideal moment to return to elective surgical activities is still uncertain. Many studies about this subject have been elaborated with many researchers and authorities involved (18). Recently, a study published in The Lancet on the detection of SARS Cov-2 viral RNA in patients healed from the disease, who had moderate (n = 46) or severe (n = 30) symptoms, demonstrated that neither group presented the viral material after the 25th day of symptom onset and that 90% of patients with mild condition tested negative for Covid-19 on the tenth day of symptom onset (19).

We believe that as there is no significant scientific evidence of viral elimination in the urine and based on the reported data on the criteria for curing the disease, elective endourological surgery in urinary lithiasis could be safely performed after 30 days at the onset of symptoms, however, we suggest that new randomized studies are taken as a reference for the topic (19). Some strategic changes to contain the spread of SARS Cov-2 can be consolidated as permanent, including in the structure of care of the operating rooms, use of computerized tools for virtual follow-up in the postoperative period and the managerial awareness of hospital resources (20).

Strategy for pre-surgical screening during Covid-19 pandemic

What should be the ideal screening of patients who undergo surgery during COVID-19 pandemic?.

Ideally, each patient should receive a telephone triage in which symptoms suggestive of COVID-19 are investigated such as cough, fever, shortness of breath, diarrhea, conjunctivitis. Telephone triage should also investigate contact with

positive or at risk COVID 19 patients. Once ruled out by telephone any symptom at the time of admission, a triage should be repeated, evaluating the possible onset of symptoms from the phone call to admission.

Considering that a large portion of the population could be COVID-19 positive but still asymptomatic, ideally each patient should enter the hospital in droplet isolation, receive two nasopharyngeal swabs and be considered positive until they have negative double swab results. Although behaving in this way, two nasopharyngeal swabs have a diagnostic accuracy of about 65%, it means that 35% of asymptomatic positive patients would not be identified. A model of this type is very difficult to realize as well as expensive and not 100% safe. Various strategies have been described so far in the literature(1, 16, 21), but no one can be considered the gold standard. In real life, telephone triage is certainly a valuable and indispensable resource in identifying suspicious cases and should certainly be pursued.

Entrance to the hospital should be permitted by a single access and subject to strict controls. At the time of admission, a triage should be repeated. Body temperature should be checked for all patients. Every patient should wear surgical masks which should be provided by the hospital and have access to 60% alcohol solutions for hand hygiene. Personal Protective Equipment (PPE) and social distance are simple and indispensable measures to avoid the spreading of the infection. A task force dedicated to COVID-19 should be set up in each hospital in order to identify and manage any suspicious case.

Visitors should be allowed to access to the hospital after strict controls just for a limited span of time and only one person for patient. They should follow the same rules of admission valid for patients.

Surgery preparation and course (Consider Covid19 negative and Covid19 patients)

First of all hospitals should be split in COVID free hospitals and COVID hospitals. COVID 19 patients should not undergo surgery except for emergencies not possible to postpone.

In case of an emergency any confirmed or suspected COVID-19 patient requiring urgent endourological surgery should be treated in a dedicated operative room (OR) with a negative pressure environment and separate access from the other ORs. For hospitals in which a dedicated OR is not available, patients should be transferred or otherwise, if not possible, all postoperative cleaning protocols should adhere to institutional central disease control instructions.

All surgeries should be performed preferably from the best surgeon available, not in learning curve, to shorten operative time and reduce complications (1, 22).

In COVID free hospitals we suggest to use the following PPE from different HWs (Table-1). The anesthesiology protocols should limit aerosolization as much as possible. PPE that anesthesiologists should use during intubation are described in Table 1. Airway management should follow strict rules leading to achieve RSI (rapid sequence intubation) to reduce aerosolization.

Extubating should be performed in OR. (High efficiency particulate air filters) HEPA should be applied on each oxygen system interface (circuit, mechanical fan) and changed for every patient. Despite overall benefit of high-flow nasal oxygen, a nasal oxygen at 3 l/min should be preferred to avoid high flow aerosol-generating technique. A disposable video laryngoscope with a separate screen should be used to minimize patient contact(23).

The sterilization of the surgical material should not be different from that usually performed even if the use of disposable instruments and equipment would be preferable. Evacuation of irrigation fluid during endourological procedures should be collected through a closed system (3).

During the outbreak of the pandemic scenario elective stone procedures such as RIRS and PCNL should be postponed. As regards the treatment of obstructive ureteral stones, ureteral stents and nephrostomy tubes insertion should be preferred to uretherolithotripsy. Not knowing how long the health emergency will last, it would be ideal to place long-lasting stents or nephrostomies so as to reduce the risk of incrustations or malfunctions of the same.

It is likely that postponing all elective interventions for stone disease will lead us to face more complex cases later and that the waiting lists become even longer than they already were. Presence of virus in urine is controversial. Viral load seems to be low but present in urine(24, 25)

Residents role

Activity reduction or suppression of outpatients and elective surgeries brought to a generalized slowdown of residents'activity (26). Surgical and academic activity of residents before the pandemic were just not ideal in most countries (27-31).

Amparore et al. found that Italian residents experienced a severe reduction or complete suppression of training exposure for clinical and surgical activities because of COVID pandemic (32).

In this scenario surgeries should be performed from the best surgeon available to shorten operative times and reduce the complications 'risk , a lack of a structured mentorship was just previously associated with an increased risk of residents 'burn out and will potentially expose residents to higher burn out risk (33).

Suggestions have been made to implement and integrate residents' activity with web platforms made available from EAU and ESU (European School of Urology) and through the use of Social Media as scientific platform (34). We believe residents in this scenario should carry on to shadow their mentors and try to get all the possible teachings from an extraordinary situation.

FOLLOW-UP OF PATIENTS

Asymptomatic patients in follow-up

Medical practices have been largely affected since the beginning of the Covid-19 pandemic, with the postponement or cancellation of medical visits. Centers severely affected by the pandemic offer consultations for follow-up of malignant diseases, and screening is carried out before the visit, so that only patients without fever or respiratory symptoms can be attended in face-to-face visits. All consultations are individual, with doctors wearing PPE. In some situations, telephone consultations and videoconferences can be used (16, 35).

Telephone consultations were also used to screen the urgency of surgical treatment. To avoid further hospital visits, imaging tests performed before the pandemic were used in conjunction with telephone consultations and routine follow--up were postponed (36).

Schedule for the follow-up visit

During the pandemic, clinics maintain daily waiting lists for patients to be treated according to internal prioritization guidelines. This procedure allows dynamically and together with other disciplines to react to changes in operational capabilities and to treat patients within the appropriate time frame. Other individual aspects must be taken into account by the physicians in charge. This includes parameters related to the patient, such as age, previous illnesses or individual opinions of the patient, as well as the consideration and availability of alternative non-operative therapies (for example, active monitoring, radiotherapy), drug therapy or neoadjuvant approaches. In addition to the transfer of urological patients to other facilities, the exchange of employees must also be considered, as it is already being prepared in many places in Germany (37).

In countries affected by the pandemic, such as Italy, hospitals were almost entirely dedicated to the treatment of patients with COVID-19, so that only emergency services were available for operated patients. It became necessary to remove urological patients across the country for emergency therapy (16). Relocating urological patients is generally much easier than removing patients with COVID-19. However, it is important to be aware of the patient's duty of care and solidarity at all times (37).

Adequate urological care should be provided to the patient, despite the fear that some have of infection or of finding an overburdened health system. Urologists need to use their communication channels to advise patients to only go to hospitals with acute complaints or in urgent cases. The dissemination of information through homepages, online portals and newsletters is an adequate action to inform patients about the avai-

lability of urological care (37). In times of general uncertainty, the appointments over the phone or online can be used as a substitute for face-to-face visits. The objective is to consider alternatives with the respective patient and define a common strategy in the current situation.

Ambulatory consultations by electronic means are inevitable in the current situation. Due to general uncertainty, many patients cancel non-urgent appointments to reduce their own risk of infection when they contact health care providers. Most patients show an understanding of the current health system situation. The inclusion in waiting lists or the allocation of future consultations can serve as an instrument for patient adequacy and safety. In many clinics, consultations for patients with tumors are now carried out exclusively by electronic means (37).

Cystoscopy and stent removal schedule

Patients who already had a ureteral stent due to complicated urolithiasis before the COVID-19 pandemic, can lead to significant morbidity, such as acute pyelonephritis, bacteremia, urosepsis and even death (38). Therefore, this subset of patients should be considered with some priority, in order to avoid a prolonged delay. The length of time the stent remains should be a factor in the prioritization process, keeping in mind that most ureteral stents can be left in place for up to 6 to 12 months. Currently, although the evidence is insufficient to support antibiotic prophylaxis in patients with long-term stents, due to the likely delays in surgery, it can be considered to reduce the risk of urosepsis and the consequent need for a mechanical ventilator (1).

The stent with external wire must be considered after procedures without complications (stone-free) to avoid a visit to the clinic for its removal. Therefore, endourologists need to be prepared to subsequently manage more difficult cases for patients whose procedure has been postponed due to lower surgical priority; in addition, if the waiting list becomes large, one can try to anticipate the procedure. However, these patients should be routinely followed up by phone calls to monitor their status (1).

Standard sterilization of the reusable endourological arsenal is also considered safe in terms of cross-contamination with COVID19, because so far the virus has not been detected in urine, although the evidence is not yet robust (39).

Follow-up tests: time in the context of the pandemic and when the outbreak goes down

Approximately 80% of patients with Covid-19 have mild disease, although the elderly and patients with comorbidities are at high risk of deterioration (40). The WHO (World Health Organization) clinical classification for the disease includes: mild disease, pneumonia and severe pneumonia, which is further categorized in adults and children (41). As most cases have mild symptoms, a high index of suspicion is required and all patients with fever and / or respiratory symptoms should be treated as having COVID-19 until proven otherwise (42). The most common symptoms include fever, cough, dyspnea, myalgia and fatigue (43). Gastrointestinal symptoms are not common, however, patients may experience nausea or diarrhea one to two days before the onset of fever and acute respiratory disease (42).

Laboratory diagnosis is necessary to confirm the diagnosis of COVID-19. The polymerase chain reaction with real-time reverse transcription (RT-PCR) is used to analyze nasopharyngeal or oropharyngeal aspirates in outpatients. In severe cases, lower respiratory samples of sputum and / or endotracheal aspirate or bronchoalveolar lavage may be used. If a patient with a high level of suspicion of COVID-19 has a negative result, additional samples should be sent (such as blood, feces and urine). To exclude COVID-19, the guidelines recommend two consecutive negative tests, which are performed at least one day apart (42, 43).

All patients prioritized for surgical procedures should be tested with nasopharyngeal aspiration for COVID-19, if possible. The maximum capacity of urological hospital beds should be reorganized to reduce the number of beds for an adequate social distance between patients (16).

The types of tests we have should take into account several parameters, such as whether the test detects the infection directly (like the virus itself) or indirectly (like host antibodies), the test response time, the ability to run multiple tests at

the same time (i.e. productivity), the need to have a minimum number of samples before testing (i.e. in batches) and the ability to perform the test in environments (44).

In order for the test results to allow for a specific clinical decision, researchers, the development of epidemiological policies and physicians need to consider each one with respect to the intention to test and the population being tested in the most specific way possible. At the moment, the detection of host-derived antibodies directed against SARS-CoV-2 will be crucial for surveillance, epidemic prediction and determination of Immunity (45).

CONCLUSION

Categorization and prioritization of patients affected by lithiasis is crucial for management, surgical selection and follow-up. Protocols, measures and additional efforts should be carried out in the current situation of the COVID-19 pandemic.

ABBREVIATIONS

RIRS = Retrograde Intra-renal Surgery
PCNL = Percutaneous nephrolithotomy
OR = Operating Room
PPE = Personal Protective Equipment
SARS-CoV-2 = Severe Acute Respiratory Syndrome–Related Coronavirus-2

CONFLICT OF INTEREST

None declared.

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Clinical and surgical assistance in prostate cancer during the COVID-19 Pandemic: implementation of assistance protocols

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ABSTRACT

Purpose: Propose an approach of prostate cancer (PCa) patients during COVID-19 pandemic.
Material and Methods: We conducted a review of current literature related to surgical and clinical management of patients during COVID-19 crisis paying special attention to oncological ones and especially those suffering from PCa. Based on these publications and current urological guidelines, a manual to manage PCa patients is suggested.
Results: Patients suffering from cancer are likely to develop serious complications from COVID-19 disease together with an increased risk of postoperative morbidity and mortality. Therefore, the management of oncological patients should be taken into special consideration and most of the treatments postponed.
In case the procedure is not deferrable, it should be adapted to the current situation. While the shortest radiotherapy (RT) regimens should be applied, surgical procedures must undergo the following recommendations proposed by main surgical associations.
PCa prognosis is generally favourable and therefore one can safely delay most of the biopsies up to 6 months without interfering with survival outcomes in the vast majority of cases. In the same way, most of the localised PCa patients are suitable for active surveillance (AS) or hormonal therapy until local definitive treatment could be reconsidered. In metastatic as well as castration resistant PCa stages, adding androgen receptor targeted agents (abiraterone, apalutamide, darolutamide or enzalutamide) to androgen-deprivation therapy (ADT) could be considered in high risk patients. On the contrary, chemotherapy, immunotherapy and Radium-223 must be avoided with regard to the consequence of hematologic toxicity and risk of COVID-19 infection because of immunodepression.
Conclusions: Most of the biopsies should be delayed while AS is advised in those patients with low risk PCa. ADT allows us to defer definitive local treatment in many cases of intermediate and high risk PCa. In regard to metastatic and castration resistant PCa, combination therapies with abiraterone, apalutamide, darolutamide or enzalutamide could be considered. Chemotherapy, Radium-223 and immunotherapy are discouraged.

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INTRODUCTION

They are called Guidelines, not God's lines

The outbreak of coronavirus that cause the disease COVID-19 has not only created a pandemic situation and a global crisis but beyond imagination, it has completely modified our way to look at medical information and its clinical application.

Medical Guidelines, without a doubt, are of utmost importance and a great deal of work is continuously deployed to offer our patients the highest level of patient care. Every society solidly invests on the training of the young generation to develop novel ideas, then exposing those ideas to a scientific method, eventually obtaining evidence and more importantly reaching a high level of recommendation. Simultaneously, our younger peers are actively taught to verify this information in detail, selecting the best of it and to create a number of standardized practices aiming to objectively guide therapeutic options. Particularly in the case of oncology there are so many exceptions that do not necessarily fit the typical case for one option or another (1). In these occasions tumor boards and faculty discussions may provide a rational and adoptable treatment option.

Nowadays days we face an unfamiliar enemy, SARS-CoV-2, an RNA virus with low mutational process but a high recombination potential allowing it to switch hosts in a rather timely fashion (2). Nevertheless, whereas we hold much basic knowledge on the anatomy of this new type of coronavirus which is able to cause severe respiratory illness in 20% of patients (5% of them requiring ventilation and intensive care) (3), no high level evidence recommendations are available to deal with the challenge it has created to humanity.

Today, we had no choice but to look back at « experience medicine » and use the creator of Sherlock Holmes, Sir Arthur Conan Doyle, approach to identify and solve problems. What do we have in our medical armamentarium that could deal with this threat? Researches around the World are dealing with this question, and of utmost importance, we must understand that during this pandemic, cancer does not stop and some specific patients still need priority treatment.

Our aim is to propose an approach for prostate cancer (PCa) patients management during COVID-19 pandemic.

MATERIAL AND METHODS

We reviewed most of the ongoing recommendations given by the main health, surgical and urological associations around the World, such as the World Health Organization (WHO), the National Comprehensive Cancer Network (NCCN), the European Association of Urology (EAU) and the British Association of Urological Surgeons (3-6). In addition, publications related to COVID-19 pandemic were also reviewed putting special interest in those focused on surgical management of patients, as well as cancer, in particularly PCa.

Afterwards, the authors propose a practical guide to manage PCa during COVID-19 outbreak based on current urological guidelines. Such proposal is adapted to the special condition we face today.

RESULTS

Patient selection to perform a PCa Biopsy and Conditions

It has been reported that SARS-CoV-2 is present in the stool of COVID-19 patients and fecal–oral transmission is possible. While it has not been demonstrated that the prostate biopsy procedure itself would be a way of COVID-19 transmission, we advise to avoid or defer almost all prostate biopsies (7-9).

Whom to biopsy

In cases where risk factors for high risk PCa are present –prostate specific antigen (PSA) >20, PSA doubling time (PSA-DT) < 6 months, suspicious of clinical T3 disease, and/or local or systemic symptoms-, biopsy can be delayed up to 3 months. On the other hand, in the absence of high risk factors, biopsy may be postponed till 3 to 6 months later (6, 8), or even 12 months according to NCCN recommendations (7) (Table-1).

In regard to Multi-Parametric Magnetic Resonance Imaging (mpMRI), the EAU recommends

Table 1 - Management of clinical suspicion of PCa and localized PCa during the COVID-19 era.

Tumor stage	Recommendations	Comments
Clinical suspicion (elevated PSA and/or abnormal DRE)	1. Presence of High risk PCa factors -PSA >20 - PSA-DT doubling time < 6 months - T3 disease, and/or local or systemic symptoms Biopsy must be delayed up to 3 months (8). 2. Absence of High risk PCa factors Biopsy may be postponed 3 to 6 months (8).	PCa prognosis generally favourable can safely delay most biopsies up to 6 to 12 months without interfering with survival outcomes in the vast majority of cases (6-8).
Localized very low, low and risk favorable intermediate-risk diseases.	AS must be prioritized while RP as well as RT should be deferred.	NCCN and EAU PCa guidelines currently recommend AS (15, 16).
Localized unfavorable intermediate risk	Delay local definitive treatment	Delay RP and RT may not imply a very high impact on oncological outcomes (13, 14).
	Start ADT 6-monthly formulations	NCCN and EAU PCa guidelines currently recommend short course of ADT added to RT (15, 16). Preoperative ADT studies show a lack of benefit in prolonging overall survival but an improvement in pathological variables (17).
Localized High-risk and very high-risk	Prioritize definitive treatment if it is available	
	Start ADT 6-monthly formulations	Initiation of ADT must be the standard of care in these patients until local therapy could be reconsidered as the coronavirus crisis improves or ends.
	Consider ADT followed by RT in selected patients	The benefit of neoadjuvant ADT has already been widely verified before RT (17).
	Consider ADT followed by RP in selected patients	Preoperative ADT studies show a lack of benefit in prolonging overall survival but an improvement in pathological variables (17).

upfront pre-biopsy mpMRI if resources allow. However, if the patient is suspected to be liable to risk of progression and metastasis, biopsy can be performed without prior MRI (6).

Considering a possible fecal-oral COVID-19 transmission no rectal lavage for preparation and complete protective personal equipment (PPE) during procedure are advisable. Negative-pressure rooms should be utilized when possible (6-9).

Patient Approach

In those patients with localized PCa, the two available options to treat them with curative intent, namely radiotherapy (RT) and radical prostatectomy (RP), must be both postponed as much as possible during coronavirus crisis (10, 11). In the case of metastatic PCa patients the use of some systemic treatments may be compromised as a consequence of an increase in the number of visits to health centers and the risk of iatrogenic infection that it would entail.

Nowadays the main question to be resolved is how long our patients can wait for a treatment without interfering with oncological outcomes. While this doubt is clarified we propose the following management.

Localized disease

Very low, low and risk favorable intermediate-risk diseases

A recent prospective, open-enrollment cohort study showed a risk of cancer death or metastasis lower than 1% over 15yr follow-up in Grade Group 1 PCa patients who underwent **Active surveillance (AS)** (12). According to this study as well as PROTECT and PIVOT trials (13, 14), NCCN and European PCa guidelines currently recommend or propose AS as a good management option in this group of patients having favorable outcomes(15, 16). Therefore, AS must be prioritized while RP as well as RT should be deferred until restrictions to contain the spread of COVID-19 are over (Table-1).

Follow-up biopsies and PSA-tests should be postponed by > 3 months from the preplanned appointment in order to decrease the number of visits to hospital and to promote social distancing (6).

Unfavorable intermediate risk

Despite the fact that AS for these stages of the disease is not contemplated in the current guidelines (15, 16), given the extraordinary situation in which we find ourselves in, RP and RT should be postponed with a believably not very high impact on specific cancer mortality (13, 14).

Short course (4-6 months) of androgen-deprivation therapy (ADT) added to RT are indicated in these patients (15, 16) while ADT prior to RP might be considered during COVID19 pandemic. Although it is well known that this last approach is not associated with survival benefits it is also related to better pathological results (17). For these reasons, we recommend the initiation of androgen blockage.

In relation to the possible effect that a prolonged neoadjuvant treatment may have on oncological outcomes it has been observed that extending neoadjuvant ADT therapy duration prior to RT from 8 to 28 weeks neither significantly improve nor worsen oncological outcomes on patients with unfavourable intermediate risk PCa (18). These results suggest that we may safely delay the need to definitive local treatment for 4-6 months (9, 18, 19) (Table-1).

Keeping into consideration that those patients with a PCa grade group 3 could have an increased risk for eventual metastases (19) as well as a five-fold increased risk of PCa mortality compared to grade group 2 (20), we suggest to continue follow-up PSA-tests every 3 months and provide the results by telehealth.

High-risk and very high-risk

Initiation of ADT must be the standard of care in these patients until local therapy could be reconsidered as the coronavirus crisis improves or ends. The benefit of neoadjuvant ADT has already been widely verified before RT (17).

In view of a lack of benefit in prolonging overall survival, current urological guidelines strongly discourage the use of elective neo-adjuvant ADT in patients who are going to undergo RP outside of clinical trials (15-17).

However, preoperative ADT studies have shown a significant reduction in positive surgical margins and downstaging along with an improvement in other pathological variables such as lymph node involvement. Additionally, these results tended to be better if neo-adjuvant ADT was prolonged from 3 to 6 or 8 months prior to surgery (17).

Intensive androgen blockage prior to RP is currently under study with favorable preliminary results, but further study is necessary (21).

In case of detecting patients with a rapid PSA-DT (≤3 months) timely therapy could be indicated and the benefits of immediate treatment must be weighed against the risk associated to iatrogenic exposure to COVID-19 (11).

As long as there is a limited availability of operating rooms, material and human surgical resources which make it impossible to perform RP, RT could be an alternative. Within RADS (Remote visits, Avoidance, Deferments, and Shortening of radiotherapy) framework created by Radiation Oncologist, shortening of the RT treatment is the fundamental principle for these high risk patients without compromising the oncological outcomes (4, 11) (Table-1).

Like what was proposed previously for patients with unfavourable intermediate-risk PCa, we suggest to maintain quarterly PSA monitoring.

Unfavourable features after radical prostatectomy

According to preliminary results from ARTISTIC meta-analysis presented at ESMO 2019 Congress, event-free survival is not improved with adjuvant radiotherapy (ART) compared to **salvage radiotherapy (SRT)** in patients with combined high-risk features (pT3-T4/R1/GS (8-10, 22). Despite ART remains the recommended treatment option until more evidence to suggest otherwise (15, 16), we strongly advise SRT as a safe alternative (Table-2).

Biochemical recurrence (BCR)

The real impact of BCR in cancer mortality is currently unknown whereas recent studies suggest that just a subgroup of patients would develop progressive disease following BCR after RP with less optimistic results in case of RT failure. In this sense, patients may be stratified into EAU Low-Risk or High-Risk BCR according to PSA-DT, pathological ISUP grade and interval to biochemical failure (23).

According to the above, in case of clinical suspicion of BCR the authors suggest to postpone complementary studies as well as salvage treatments during COVID-19 pandemic, especially in

Table 2- Management of unfavourable features after radical prostatectomy or biochemical recurrence after local treatment of PCa during the COVID-19 era.

Tumor Stage	Recommendations	Comments
Unfavourable features after radical prostatectomy	Avoid adjuvant RT.	According to ARTISTIC meta-analysis, event-free survival is not improved with ART compared to SRT in patients with combined high-risk features (pT3-T4/R1/GS 8-10) (22).
Biochemical recurrence	Delay complementary studies as well as salvage treatments, especially in EAU low-risk cases. Offer salvage treatment for those patients with high-risk BCR if it is available. If not, neoadjuvant ADT could be considered (6).	Recent studies suggest that just a subgroups of patients would develop progressive disease following BCR after local treatment (23).

RT = Radiotherapy; **ART** = Adjuvant Radiotherapy; **SRT** = Salvage Radiotherapy; **EAU** = European Association of Urology **BCR** = Biochemical Recurrence; **ADT** = Androgen deprivation therapy

Low-Risk cases. On the other hand, we propose to offer salvage treatment for those patients with High-Risk BCR if it is available. If not, neoadjuvant ADT could be considered (6) (Table-2).

Non metastatic castration- resistant prostate cancer

Three randomised phase III trials, PROSPER, SPARTAN and ARAMIS showed a significant metastatic free survival benefit in non-metastatic castration- resistant PCa patients treated with enzalutamide vs. placebo, apalutamide vs. placebo or darolutamide vs. placebo, respectively. Therefore, current guidelines strongly recommend these drugs to patients with castration- resistant PCa, absence of metastases and PSA-DT < 10 months. Taking into account that survival benefit was not proven after 20 months of follow-up as well as potential adverse events, we recommend these drugs in high selected patients during the COVID-19 pandemic (1, 15, 16) (Table-3).

Metastatic disease

Metastatic castration- sensitive prostate cancer

ADT must be initiated according to current standard of care (15, 16), with the six-month formulations being the best choice (4, 5).

In regard to Intermittent ADT, it requires a closer PSA and testosterone monitoring in addition to possible images so it should be avoided in order to minimize hospital attendance.

In the last few years combination castration therapy with the new hormonal treatments (abiraterone, apalutamide or enzalutamide) has demonstrated benefits in terms of survival compared to ADT alone. Abiraterone acetate and prednisone or apalutamide added to ADT significantly reduce the risk of death by an amount equal to 28 and 33% respectively (24, 25) while enzalutamide plus ADT reduces radiographic progression-free survival or deaths by 60% (26).

The median age of patients who are candidates for combination hormonal treatments is around 70 (24-26). Although age is a potential risk factor for mortality of adult inpatients with COVID-19 (27) and these new drugs imply a closer follow-up, agreeing with the EAU, we suggest to offer immediate systemic treatment within < 6 moths as long as a correct follow-up by telemedicine can be guaranteed (6).

In case the use of combined hormonal treatment is contemplated, we suggest to avoid abiraterone since the use of corticosteroids in population infected with SARS-CoV-2 is not yet completely clarified (5, 28).

With respect to chemotherapy, it must be avoided as much as possible being replaced by ADT or ADT in combination with androgen receptor targeted agents in order to reduce the number of clinical visits and haematological toxicity without compromising oncological outcomes (Table-4).

Metastatic castration- resistant prostate cancer

For castration-resistant metastatic patients, ADT must be maintained.

Abiraterone significantly improves overall survival among patients who previously receive chemotherapy compared to ADT alone. Nevertheless, improvement in median survival is not more than 5 months (29). In those patients who have not received chemotherapy, median overall survival is also improved from 30,3 to 34,7 months (30). Similar results are observed with enzalutamide plus ADT. It has been reported an improvement

Table 3 - Management of non metastatic castration- resistant PCa during the COVID-19 era.

Tumor Stage	Recommendations	Comments
Nonmetastatic castration- resistant prostate cancer	Consider combination castration therapy with the new hormonal treatments (apalutamide, darolutamide, enzalutamide) in high selected patients.	These drugs have demonstrated benefits in terms of metastatic free survival in patients with PSA-DT < 10 months (1, 15, 16).

PSA-DT = Prostate Specific Antigen - Doubling Time

Table 4 - Management of metastatic PCa during the COVID-19 era.

Tumor stage	Recommendations	Comments
Metastatic castration-sensitive prostate cancer	ADT 6-months formulations must be initiated.	ADT is the current standard of care (15,16).
	Avoid intermittent ADT.	Intermittent ADT requires a closer PSA and testosterone monitoring in addition to possible images.
	Consider combination castration therapy with the new hormonal treatments (abiraterone, apalutamide or enzalutamide).	These drugs have demonstrated benefits in terms of survival compared to ADT alone (24-26).
	Prefer apalutamide or enzalutamide to abiraterone.	Effect of corticosteroids in population infected with SARS-CoV-2 is not yet clear (5, 28).
	Avoid CTx.	CTx is associated with hematological toxicity and implies multiple visits to the hospital (6).
Metastatic castration-resistant prostate cancer	ADT 6-months formulations must be maintained.	ADT maintenance is the current standard of care (15,16).
	Consider combination castration therapy with the new hormonal treatments (abiraterone, enzalutamide).	These drugs have demonstrated benefits in terms of survival compared to ADT alone (29, 30-32).
	Prefer enzalutamide to abiraterone.	Effect of corticosteroids in population infected with SARS-CoV-2 is not yet clear (5, 27).
	Avoid CTx.	CTx is associated with hematological toxicity and implies multiple visits to the hospital (6).
	Avoid Immunotherapy (Sipuleucel-T).	Sipuleucel-T might cause cytokine release while cytokines as IL-6 have been directly related to the most aggressive forms of COVID-19 (4, 34).
	Avoid Radium-223.	Radium-223 is associated with overall survival benefit by 3,6 (in the absence of visceral metastases) compared to ADT alone, but it is also associated to hematologic toxicity (35).
	Avoid starting denosumab or zoledronic acid.	Denosumab or zoledronic acid have no impact on overall survival but could generate osteonecrosis of the jaw or hypocalcaemia (36, 37).
	In those patients under treatment, denosumab may be maintained while zoledronic acid should be delayed.	Denosumab can be administrated in its monthly subcutaneous formulation while zoledronic acid requires monthly hospital intravenous administration.

in median overall survival of 5 months in those patients already treated with chemotherapy(31) and 2 months in chemo-naïve patients (32).

In case we decide to introduce abiraterone or enzalutamide, we must choose enzalutamide for the reasons previously mentioned (5, 27).

Chemotherapy also increases median survival in this type of patient, but we advise against its use during the current crisis (4-6, 33).

Cytokines as IL-6 have been directly related to the most aggressive form of COVID-19. Hence, Immunotherapy with sipuleucel-T whose more frequently adverse events involve cytokine release, should not be given (4, 34).

Radium-223 must be further avoided. Although, it is associated with overall survival benefit by 3,6 months in patients with CRPC without visceral metastases compared to ADT alone, it is also associated to hematologic toxicity (anemia, thrombocytopenia and neutropenia) and monthly risk visits to hospital for intravenous administration (35).

As a result of the lack of benefit in overall survival with the administration of denosumab or zoledronic acid we propose to delay its introduction due to their potential toxicity (e.g., osteonecrosis of the jaw, hypocalcaemia) (36, 37). In those cases where treatment has been already started, denosumab can be maintained in its monthly subcutaneous administration while zoledronic acid, which requires monthly hospital intravenous administration, should be delayed (Table-4).

DISCUSSION

PCa is the second most common cancer in men worldwide (behind lung cancer) and the first one in Europe with a higher incidence in developed countries as a consequence of screening programs (38). Therefore, this pathology represents an important percentage of the burden of work carried out in Uro-Oncology units, being RP one of the most frequent operating room procedures performed by urologists with a rising trend during recent years (39).

While the management of PCa was already complex and under constant debate (15, 16), the current global pandemic has further complicated the treatment algorithm of this pathology. Additionally, all current recommendations are not based on robust evidence, but mostly expert consensus. In this sense, at most the PCa treatment recommendations in "EAU guidelines recommendations to the COVID 19 era" have level 2-3 evidence (6).

Elective definitive PCa treatments as RP as well as RT are being cancelled or postponed for an unknown time in view of the following points:

1. Patients suffering from cancer are at increased risk of infection and serious complications from COVID-19 (40).
2. Unknown SARS-CoV-2 infected patients who are asymptomatic and who have undergone a surgery are more likely to suffer from complications with a mortality rate of 20.5% (41).
3. Risk of SARS-CoV-2 infection in the surgical team as well as patients (iatrogenic exposure to the virus).
4. Need of hospital resources as PPE, Hospital/ICU beds and ventilators.

In regard to definitive treatment choice, we must keep in mind that replacing most of RP by RT could not be the universal solution. In a well-balanced scenario, both treatments coexist and resources should be adapted to needs. Supposing that all patients suitable to undergo active treatment are treated with RT, treatment waiting time would be dramatically increased resulting in treatment delay. The potential solution may create a new problem. Hence, we advise to considerer RP as a potential curative treatment during and after COVID 19 pandemic. In this sense, it has been shown that in localized low and intermediate-risk PCa patients, 6 to 9 months of delay from biopsy to RP is associated to an increased risk of BCR or clinical recurrence at 5 years lower than 18% and 0.6%, respectively. While in high risk patients the risk of BCR is higher (close to 24% after 9-12 from the biopsy), short term ADT might protect them until surgery in 3-6 months (42). It is important to take into consideration that the studies which lead us to avoid ADT prior to RP due to a lack of survival benefit (neither a detriment) compared to immediate surgery are the same which support the use of neoadjuvant ADT in those patients whose surgery is forced to be delayed during COVID19

pandemic (20).

The special situation that urologists face today force all of us not only to think about when but also how we must treat our patients.

All elective visits should be postponed or transitioned to telehealth visits to further reduce exposure risk. For those patients who must be seen in clinic, social distancing should be promoted to ensure minimal contact with staffs and other patients (43).

Once SARS-CoV-2 was confirmed as global pandemic by WHO, and community transmission was accepted, all patients must be considered suspected cases until proven otherwise. Therefore, we consider that all patients should be tested prior to any surgery. In case it is not possible, telephone interview depicting symptomatic or oligo-symptomatic cases could be an alternative option (9, 44). Additionally, in those case where abdominal tomography image is required, thorax imagine should be added at the same time.

Testing of elective patients is recommended within 48 hours prior to surgery. SARS-CoV-2 positive patients or clinically suspected patients should have their CaP intervention postponed as far as possible (6).

Several studies have proven transmission of different viruses during surgery (45, 46). According to a recent publication, this risk could be higher during laparoscopic procedures compared to open ones (47). This is due to the concentrated aerosol in the abdominal cavity formed during the operation being released suddenly when trocars are removed, small incisions are done or instruments are exchanged (48). In addition, airborne transmission is possible through intubation and extubation. This fact has led the EAU Robotic Urology Section to propose some recommendations to safeguard the health of the surgical staff (9).

However, we shouldn't forget that not all urological cancers are PCa. The extent of therapeutic alternatives for PCa in its different stages drive us to considerer all of them during the lack of medical and surgical resources in favour of non-deferrable treatments such as cystectomies, trans-urethral resection of high volume tumours, big mass nephrectomies, or orchiectomies.

CONCLUSION

As a consequence of COVID-19 pandemic several measures have been taken in order to reduce the fast spread of the virus, to protect health professionals from infection during their work, to guarantee the health of in-patients, and to ensure the availability of health resources to address the vast number of patients suffering from the coronavirus disease. Subsequently, clinical and surgical strategies in Urology have been forced to adapt to the changes brought about by COVID-19.

Since PCa prognosis is generally favorable, we can safely delay most of the biopsies while AS must almost be mandatory in those patients with low risk PCa. Furthermore, the existence of therapeutic alternatives such as ADT allows us to defer definitive local treatment in many cases of intermediate and high risk PCa, assuming a believably not too significant impact on oncological outcomes. In regard to metastatic castration resistant PCa, combination therapies with novel drugs such as abiraterone, apalutamide, darolutamide or enzalutamide should be considered in high risk diseases whereas their secondary effects could be managed by telehealth. Chemotherapy or Radium-223 must be avoided because of haematological toxicity and frequent hospital visits. We advise against the use of Sipuleucel-T given the risk of cytokines reaction.

Nevertheless, each PCa case must be considered individually and the proposed recommendations should constantly adapt to the epidemiological evolution of the situation.

ABBREVIATIONS

PCa = Prostate Cancer
CRPC = Castration Resistant Prostate Cancer
RT = Radiotherapy
RP = Radical Prostatectomy
ADT = Androgen Deprivation Therapy

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Bladder Cancer at the time of COVID-19 Outbreak

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ABSTRACT

The COVID-19 outbreak has led to the deferral of a great number of surgeries in an attempt to reduce transmission of infection, free up hospital beds, intensive care and anaesthetists, and limit aerosol-generating procedures. Guidelines and suggestions have been provided to categorize Urological diseases into risk groups and recommendations are available on procedures that can be or cannot be deferred. We aim to summarise updates on diagnosis, treatment and follow up of bladder cancer during the COVID-19 outbreaks.

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INTRODUCTION

The coronavirus disease 2019 (Covid-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has had major effects on individuals and healthcare systems (1). The virus was detected in Wuhan, China in December 2019 and as of May 10 2020, there are over 4.1 million cases and over 280,000 deaths worldwide (2). Protocols have been derived to limit hospital access and reduce services in an attempt to reduce transmission of infection, free up hospital beds, intensive care, anaesthetists and limit aerosol-generating procedures.

Urological diseases have been categorised into risk groups and recommendations are available on procedures that can be or cannot be deferred (3, 4). Out-patient consultations are preferred to be performed through telemedicine. A recent study of 399 urology patients showed that 63.2% were eligible for telemedicine and 84.7% preferred a telemedical consultation during the COVID-19 period (5).

There are certain factors that affect the choice of different urological procedures such as the need for post-operative intensive care, the need for blood products and cardiovascular or respiratory co-morbidities. Patients with COVID-19 and multiple co-morbidities tend to have poorer outcomes (6, 7).

Here, we discuss the impact and changes imposed on bladder cancer (BC) management.

Bladder cancer epidemiology and classification

Bladder cancer is the 10th most common cancer worldwide, with an estimated 549,000 new cases and 200,000 deaths. Both the incidence and mortality is higher in men (8). Interestingly, men are more affected with COVID-19 and are more likely to get more severe disease (9). Tobacco smoking and occupational exposure to carcinogens are the factors with the highest attributable risk (10). However, there is increasing evidence to suggest the role of genetic polymorphism. The Cancer Genome Atlas (TCGA) provided molecular characterisation of BC based on somatic changes, with FGFR3 and KRAS implicated (11).

Approximately 75% of BC is non-muscle invasive (NMIBC) and include disease confined to the mucosa, pTa, carcinoma in situ (Cis) or to the submucosa, pT1. Muscle invasive BC (MIBC) accounts for 25% of BC diagnosed. The WHO grading system categorise BC into papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade (LG) and high-grade (HG) papillary urothelial carcinoma. Urothelial cell carcinoma (UCC) is the most common histological type. A subgroup of variants with worse prognosis has been described, which include micropapillary UCC, nested variant and microcystic UCC, plasmacytoid, small-cell carcinoma, sarcomatoid and the presence of lymphovascular invasion (LVI) (12). Stratification of BC based on molecular classification has been investigated and although appear promising, it is currently not mature enough for routine clinical application (13). There are three risk groups of BC, based on predicted recurrence and progression rate derived from the European organization for research and treatment of cancer (EORTC) (13). Low-risk (LR) BC include primary, solitary, pTaG1 (PUNLMP), <3cm, no Cis; high-risk (HG) include pT1, G3 (HG), Cis, multiple, recurrent and >3cm pTaG1-2/LG tumours; and intermediate-risk include tumours not defined in the low and high-risk groups. A subgroup of highest-risk tumours includes G3pT1/HG with Cis, multiple and/or large G3pT1/HG and/or recurrent G3pT1/HG, G3pT1/HG with prostatic urethra Cis and some forms of variant histology of urothelial carcinoma and LVI.

EAU diagnostic guidelines prior to COVID-19

The European Association of Urology (EAU) recommend investigating BC with urinary cytology, CT urogram, flexible-cystoscopy and transurethral resection of the bladder tumour (TURBT), the latter can be both diagnostic and therapeutic for NMIBC (12, 14). Urinary molecular markers such as UroVysion (FISH), Nuclear Matrix Protein 22 (NMP) and fibroblast growth factor receptor 3 (FGFR)/telomerase reverse transcriptase (TERT) have not been accepted for diagnosis or follow up in routine practice or clinical guidelines. Confirmed MIBC should be staged with CT thorax--abdomen-pelvis (TAP).

EAU diagnostic recommendations during COVID-19

The EAU categorised diagnoses into four priority groups, defined as the following (15):

1) Low priority, clinical harm (progression/metastasis) very unlikely if service postponed by 6 months.

2) Intermediate, clinical harm possible if postponed 3-4 months, but unlikely.

3) High, clinical harm and cancer-related deaths very likely if postponed >6 weeks.

4) Emergency, life-threatening situation on opioid-dependent pain.

NMIBC

LG NMIBC has a low cancer-specific mortality rate of around 1-2%, therefore, active surveillance is an appropriate management option (16). 1) low priority diagnostics can be deferred by 6 months; 2) intermediate priority, diagnosed before end of 3 months; 3) high priority, diagnosed within <6 weeks which include CT urogram and USS in patients with visible haematuria (VH) and cystoscopy in patients with VH without clots; 4) emergency, diagnosed within <24 hours which include TURBT in patients with VH and clot retention requiring bladder catheterization (15).

MIBC

The diagnosis of low priority cases can be deferred by 6 months and intermediate priority

cases before the end of 3 months. High priority cases should be diagnosed within <6 weeks and include MIBC staging with CT TAP.

Alternatives

Although current diagnostic tools include urinary cytology, imaging, flexible-cystoscopy and TURBT, this may be the time to utilize molecular markers and next-generation sequencing to aid in the diagnosis and predicted outcome of NMIBC (17,18).

EAU treatment guidelines prior to COVID-19

The management of BC is based on histology, grade and stage, patient's co-morbidities and performance status and patient's preference. NMIBC are given a single mitomycin instillation preferably in the first few hours following TURBT. Some histological confirmed tumours are subject to re-resection such as, HG, pT1, incomplete or no muscle obtained in the first resection (19). Following TURBT, low-risk NMIBC can be managed with cystoscopic surveillance at 3 and 12 months after diagnosis followed by annual cystoscopies for five years. High-risk NMIBC have the option of Bacillus Calmette-Guérin (BCG) intravesical instillations or radical cystectomy (RC) (20). MIBC are managed with cisplatin-based neoadjuvant chemotherapy (NAC) followed by RC and pelvic lymph node dissection (PLND) or bladder-sparing modalities including radiotherapy and chemotherapy as part of a multimodal treatment (21). Metastatic BC are managed with cisplatin-based chemotherapy such as gemcitabine, cisplatin (GC), methotrexate, vinblastine, adriamycin, cisplatin (MVAC), paclitaxel, cisplatin, gemcitabine (PCG) and/or immunotherapy with checkpoint inhibitors (programmed death ligand 1).

EAU treatment recommendations during COVID-19

NMIBC

Low priority cases can be deferred by 6 months and include: 1) TURBT in patients with small papillary recurrence/s, <1cm and pTa/1 LG tumours, re-resection in patients with visibly complete initial TURBT of pT1 lesion with muscle in the specimen; 2) early post-operative chemotherapy instillation in presumably low/intermediate--risk tumours; 3) intravesical BCG or chemotherapy instillations in patients with intermediate-risk NMIBC (15, 16).

Intermediate priority cases should be treated before the end of 3 months and include: 1) TURBT in patients with any primary tumour or recurrent tumour >1cm without VH or history of HR-NMIBC; 2) immediate RC in patients with highest-risk NMIBC; 3) early RC in patients with BCG unresponsiveness or failure (15, 16).

High priority cases should be treated within <6 weeks and include: 1) TURBT in patients with bladder lesion and intermittent VH or a history of HR-NMIBC; 2) re-resection in patients with visibly residual tumour after initial TURBT and large or multiple HGpT1 at initial resection without muscle in the specimen; 3) induction intravesical BCG ± first maintenance therapy (6 + 3) in patients with HR-NMIBC. HR-NMIBC progress to muscle invasion or metastatic disease in 15-40% of patients and 10-20% may die from BC. Therefore, BCG is the preferred choice for most patients and maintenance therapy can be resumed when COVID-19 subsides (15, 16). Emergency priority cases should be treated within <24 hours and include TURBT in patients with VH with clot retention requiring bladder catheterization (15).

MIBC

Prolonged delays (>90 days) between TURBT and RC are associated with poor survival. Russell et al. found a significant risk of death for patients in which treatment was delayed (HR 1.34, 95%CI 1.18-1.53) (22). Lin-Brande et al. explored patients with variant histology undergoing RC and reported a significant increase in the risk of death in patients in whom surgery was delayed beyond 12 weeks (HR 3.45, 95% CI 1.51–7.86) (23). Kulkarni et al. reported a rise in the risk of death when there was a delay of >40 days between TUR and radical cystectomy (24). Although in patients who undergo NAC the delay between diagnosis and RC becomes less significant, the time between NAC and surgery has been explored as a risk factor for mortality. Boeri et al. reported a decreased survival for patients in whom this time frame was >10 weeks, with a 3-year survival of 64% vs 42% for

patients operated, 10 weeks and >10 weeks respectively (25). Moreover, delay in surgery has been associated with an increased risk of upstaging (26, 27). Thus, EAU guidelines recommend RC to be performed within 12 weeks. Therefore, during the pandemic, RC delays for MIBC of up to 12 weeks may be safe.

In low priority cases, consider omitting NAC (cisplatinum-eligible only) in T2-3 focal N0M0 patients. The proven benefit of NAC on T2 disease has to be weighed against the risks (15).

Intermediate priority cases should be treated before the end of 3 months and include: 1) offering RC in T2-4a, N0M0 tumours; 2) multimodal bladder-sparing therapy can be considered for selected T2N0M0 patients; 3) chemoradiation should be offered to improve local control in cases of inoperable locally advanced tumours. In cT4 or N+, radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome (15, 16).

High priority cases should be treated within <6 weeks and include: 1) TURBT for suspicious invasive tumour identified on imaging; 2) consider alternatives such as radiotherapy ± chemotherapy to palliative RC; 3) NAC for individualize risk in high burden T3-4 N0M0 patients while they are on the waiting list; 4) offer adjuvant cisplatin-based combination chemotherapy to patients with T3-4 and/or pN+ disease if no NAC was given (15, 16).

Emergency cases include: 1) radiotherapy ± chemotherapy for intractable haematuria with anaemia; 2) nephrostomy for locally advanced BC with acute renal failure; 3) embolization or haemostatic radiotherapy for bleeding with haemodynamic repercussion (15).

Surgeons must consider that RC is a morbid surgery, with a risk of transfusions of 5-25% (28), as well as a non-negligible risk of Clavien IIIb complications (29) requiring further operating room occupation and eventual need for intensive care. Clearly, in times when intensive care units may be fully occupied during the COVID-19 pandemic, one must ask whether RC can be safely performed.

A thorough discussion with the patient should be carried out concerning the type of urinary diversion. Orthotopic neobladder reconstruction has been systematically associated to increased hospital stay and post-operative complications (30). Thus, although each patient does require specific decision making, a trend towards increased implementation of non-continent urinary diversion is probable. Furthermore, minimally invasive surgery, and in particular robotic-assisted radical cystectomy (RARC) is increasingly being implemented across urology departments in the effort to reduce the significant morbidity of radical cystectomy. Although results are contradictory (31), randomized controlled trial exploring RARC with extracorporeal urinary diversion did not find a significant reduction of post-operative complications (32). However, supporters of the robotic approach claim that an intracorporeal diversion (33) may indeed impact positively on the patients' recovery after surgery, hence one could speculate that RARC with intracorporeal urinary diversion could be an intriguing solution during the pandemic. However, the safety of the surgical team during laparoscopic surgery must be kept in mind, adopting the adequate protective equipment for surgeons involved in RARC, managing correctly the insufflation and exsufflation of pneumoperitoneum and limiting this surgery to expert centers.

Trimodal therapy (TMT), consisting of complete TURBT, chemotherapy and radiotherapy is an interesting alternative to surgery in selected patients (21). Studies have demonstrated its equivalence to RC in terms of oncologic outcomes (34). At a first glance, one could support the superiority of TMT over surgery during the outbreak, given its improved safety and reduced risk of complications, need for transfusion or occupation of intensive care units. However, one must consider that TMT requires a complete TURBT, 40-46 Gy radiation therapy, platinum-based chemotherapy and frequently, an additional TUR under general anaesthesia before receiving tumour boost radiation therapy of 20 Gy. This accounts for multiple accesses to a tertiary referral center, with a consequent increased risk of exposure to COVID-19, in patients potentially immunosuppressed due to chemotherapy. Therefore, although its undeniable benefits in terms of morbidity, TMT does indeed increase the number of accesses and transportations of patients to hospitals, potentially overcoming its benefits.

Adjuvant chemotherapy has an uncertain clinical benefit (35). On the other hand, it is associated with immunosuppression and increased risk of infective complications and as such, it should be avoided in times of COVID19.

Metastatic BC

Intermediate priority cases require assessment of risk and benefit. Asymptomatic patients with low disease burden can postpone treatment (8-12 weeks) under clinical surveillance. Treatment include: 1) cisplatin-based combination chemotherapy; with GC, MVAC, preferably with G-CSF, high-dose MVAC with G-CSF or PCG; 2) offering checkpoint inhibitors depending on PD-L1 status; 3) offering checkpoint inhibitor to patients progressing during or after platinum-based combination chemotherapy.

High priority cases should be treated within <6 week: 1) G-CSF should be considered for symptomatic patients; 2) cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, high-dose MVAC with G-CSF or PCG; 3) offer checkpoint inhibitors depending on PD-L1 status (15).

A regime comprising GC with G-CSF rather than MVAC may be preferred due to the higher likelihood of neutropenia in patients receiving MVAC (36).

EAU follow up guidelines prior to COVID-19

NMIBC

Patients with LR pTa tumours should undergo cystoscopy at 3 and 12 months following diagnosis and yearly for 5 years. Patients with HR NMIBC should undergo cystoscopy every 3 months for 2 years, every 6 months until 5 years and then yearly thereafter. Patients with intermediate risk tumours should have an in-between (individualized) follow-up scheme. Rigid cystoscopy and bladder biopsies should be performed when check flexible cystoscopy shows suspicious findings. Those who are on maintenance BCG undergo interval check cystoscopies and biopsies (14).

MIBC

Patients who underwent RC should have a CT scan every 6 months until the third year, followed by annual imaging thereafter to monitor for local and upper tract recurrences. Those who received radiotherapy should undergo cystoscopic surveillance as per the HR-NMIBC protocol (12).

EAU follow up recommendations during COVID-19

NMIBC

Low priority cases are deferred by 6 months and follow up include: 1) cystoscopy in patients with a history of low/intermediate-risk NMIBC without haematuria; 2) upper tract imaging in patients with a history of HR-NMIBC (15).

Intermediate priority cases should be followed up before the end of 3 months cystoscopy in patients with a history of HR-NMIBC without haematuria.

High priority cases should be followed up within <6 weeks with cystoscopy in patients with NMIBC and intermittent haematuria.

Emergency cases should be followed up within <24 hours with cystoscopy or TURBT in patients with VH with clots.

MIBC

Routine follow up periods after RC should be extended to 6 months (15).

CONCLUSION

During the COVID-19 outbreak it is safe to postpone surveillance and TURBT for low and intermediate risk BC. Patients presenting de novo haematuria should undergo urinary cytology, USS kidney-ureter-bladder or clinical cystoscopy to assess their risk status. BCG induction and one course of maintenance should be offered as first line treatment in patients with HG-NMIBC. Re-resection should be limited to more aggressive cases or when the risk of residual tumour is present. Higher risk cases should undergo RC if hospital capacity and COVID-19 burden allows. RC can be delayed by up to 12 weeks without causing harm to the patient. NAC should be considered balancing benefits from the therapy and risks for immunosuppression. TMT may have a potential role according to the facility of the hospital.

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Consideration in the management of renal cell carcinoma during the COVID-19 Pandemic

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ABSTRACT

Introduction: Recently the COVID-19 pandemic became the main global priority; main efforts and health infrastructures have been prioritized in favor of COVID-19 battle and the treatment of benign diseases has been postponed. Renal cell cancer (RCC) patients configure a heterogenous populations: some of them present indolent cases which can safely have postponed their treatments, others present aggressive tumors, deserving immediate care. These scenarios must be properly identified before a tailored therapeutic choice.

Objectives We propose a risk- based approach for patients with RCC, to be used during this unprecedented viral infection time.

Materials and Methods: After a literature review focused in COVID-19 and current RCC treatments, we suggest therapeutic strategies of RCC in two sections: surgical approach and systemic therapy, in all stages of this malignance.

Results: Patients with cT1a tumors (and complex cysts, Bosniak III/IV), must be put under active surveillance and delayed intervention. cT1b-T2a/b cases must be managed by partial or radical nephrectomy, some selected T1b-T2a (($\leq$7cm) cases can have the surgery postponed by 60-90 days). Locally advanced tumors ($\geq$cT3 and or N+) must be promptly resected. As possible, minimally invasive surgery and early hospital discharge are encouraged. Upfront cytoreduction, is not recommendable for low risk oligometastatic patients, which must start systemic treatment or even could be put under surveillance and delayed therapy. Intermediate and poor risk metastatic patients must start target therapy and/or immunotherapy (few good responders intermediate cases can have postponed cytoreduction). The recommendation about hereditary RCC syndromes are lacking, thus we recommend its usual care. Local or loco regional recurrence must have individualized approaches. For all cases, we suggest the application of a specific informed consent and a shared therapeutic choice.

Conclusion: In the pandemic COVID -19 times, a tailored risk-based approach must be used for a safe management of RCC, aiming to not compromise the oncological outcomes of the patients.

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INTRODUCTION

Renal cell carcinoma (RCC) is one of most lethal urologic tumors, accounting for 2-3% of all adult malignances. In the 2018 there were 415,000 new cases and 180,000 deaths by this RCC in the World. In the global scenario, the incidence, mortality and prevalence of RCC in Latin America and Caribe corresponds respectively to 7,9% (31,983 cases); 8.2% (14,288) and 7,6% (77682 cases) of World total rates (1) RCC incidence is increasing, and its main risks factors are competing with the higher risks groups for COVID 19 infection and complications: age >60 years, arterial hypertension, diabetes, obesity, smoking (2). Thus, during this pandemic time, many patients diagnosed with RCC, if immediately treated by inpatient procedures (as surgery) are under risk of developing this viral infection and its life-threatening complications (3).

Based on reports from first countries affected by this infection, health authorities, and medical societies, in these times, the main efforts and health infrastructures must be prioritized in favor of COVID-19 battle, reserving in advance, hospital health care facilities, personal protection equipment, and human resources that must be dedicated for pandemic cases. Concomitantly, surgeries for benign affections has been postponed. Regarding oncological patients (in this text we are focused only in RCC) there are challenging tasks: we must develop individualized risk-based therapeutic strategies aiming do not compromise the oncologic outcomes of the distinct risk groups of RCC patients. We must identify cases of RCC with reduced potential of biologic aggressiveness. These patients can be spared from infectious risks associated with immediate surgeries, and we must postpone their treatments. Conversely, it is essential to indicate prompt surgical or systemic treatment for patients presenting with advanced life-threatening tumors despite of actual virus risks.

For patients by personal reasons that are not able to postpone their treatments, individualized shared decision between them, their relatives and physicians must be done after an extensive discussion evolving risks and benefits.

Based on recent information about oncological management of cancer in the new coronavirus era, and the natural history of RCC and best practices of its treatment, we proposed a risk-adapted approach of patients with RCC.

In all mentioned situations, we recommend the signature of a specific informed consent document focused on the adapted risks of RCC managing in COVID-19 times.

All recommendations in this manuscript are for patients not infected by COVID 19. For patients infected, or under suspicion of this infection, and requiring prompt oncologic treatments, we must wait the recovery of the infection to start surgery or systemic approach. Emergency patients must be operated following strict protection recommendations.

MATERIALS AND METHODS

We reviewed the recent literature (until April 2020 30Th) in English, Spanish and Portuguese Languages, searching by the mesh terms: COVID-19, coronavirus and renal cell carcinoma, kidney cancer, renal cancer, surgery, nephrectomy, ablation, active surveillance, systemic therapy, immunotherapy, target therapy, adjuvant, neoadjuvant.

We discuss the therapy of RCC in two sections below: surgical approach, systemic therapy.

RESULTS

Surgical Approach

Surgery (radical nephrectomy, partial nephrectomy) is the most effective treatment for localized and locally advanced tumors and for some selected metastatic cases. Here, we discuss alternatives for small renal masses (SRM), localized tumors, local advanced tumors, and metastatic patients (4).

Small Renal masses (tumors ≤ 4.0 cm, and complex renal mass Bosniak II/IV) (cT1aN0M0)

SRM configures a heterogeneous group of lesions with distinct aggressiveness: around 20% correspond to benign lesions, around 60% are RCC with low malignance potential (low grade and fa-

vorable histopathologic features), and stage cT1N-0M0 staging. These patients, and patients with Complex Cysts (Bosniak III/IV) must be put under active surveillance (AS) with a cross sectional image exam being required in 6-8 months. After the pandemic control they must be treated. For elderly or sick patients, the watchful waiting (WW) is the best approach, avoiding image or laboratory tests. Few SRM (10-20%) can be higher risk tumors (high grade, necrose, aggressive histology). Regarding of these factors, the majority of malignant SRM grows at a rate of few mm/year, and in face of these, it seems safe to maintain these patients under AS, during the estimated few months of the viremia peak and avoid renal biopsy in this moment (5, 6).

Exceptions: as some of SRM patients may be refractory, or due to personal reasons are not available to be under AS protocols, we can offer outpatient percutaneous ablation (cryotherapy or radiofrequency), which are as effective as partial nephrectomy (PN), for lesions ≤ 2.5-3.0. For lesions between 3-4.0 cm, PN present best oncological results and can be offered, preferentially by minimally invasive PN (videolaparoscopy, robotic PN, or open PN by mini-incisions (7)), aiming prompt hospital discharge (24h).

Localized RCC (cT1b:4.0-7.0cm and cT2 N0M0)

Patients presenting cT1b (and some selected T2a< 7.0 cm) lesions without clinic and radiologic evidence of aggressive disease may be safely have postponed their surgeries for around 60-90 days (an image exam (TC or MRI) may be desirable after this time). In this conditions elderly and sick people, must be put under WW. Few young and health patients and patients afraid of postponement, exceptionally, could be ordered an outpatient percutaneous renal mass biopsy: If they present low aggressive lesions (low grade clear cell RCC, Papillary Type 1, chromophobe RCC e.g.), they might be recommended to delay the surgery. If biopsy reveals aggressive patterns or patient is refractory, surgery can be offered. Majority of patients with cT2 lesions must undergo immediate surgery. If they are unfit to surgery, or present co-morbidities which put them under higher risk of COVID-19 infection and complications, we can discuss WW or exceptionally a decision based on their biopsy finding (not for unfit, only for refractory patients). In these cases, the choice between PN or radical nephrectomy is a surgeon's decision-making process, based on his personal skills, the tumor morphometry, patient health status, institutional infrastructure resources, patient preferences, etc. In all cases it will be recommended whenever possible minimally safe invasive approaches (protection against aerosols) and early hospital discharge.

Locally advanced disease or metastatic lesions (T3-4, and/or N+M0)

Patients with localized advanced RCC, presenting invasion of perirenal fat, renal sinus, excretory system, regional lymph nodes, renal vein, vena cava thrombus or adjacent invasions demand immediate surgical resection. The majority of these require radical nephrectomy (RN), with regional lymphadenectomy and/or wide regional excision. Few SRM (10-15%) can be invasive (cT3) (8) demanding prompt resection. Efforts for early hospital discharge must be pursued.

Metastatic cases

Patients presenting poor risk or intermediate risk metastatic RCC according to IMDC- International Metastatic Disease Consortium or MSKCC – Memorial Sloan Kettering classifications - seem to have no advantage with upfront cytoreduction (9, 10) and they must receive systemic treatment, which will be discussed in the next section. Although low risk oligometastatic patients can be satisfactory undergo upfront surgery with or without resection of metastasis, we think during the coronavirus time, the upfront surgery must be avoided. Low risk and selected intermediated risk patients can start systemic therapy and must be reevaluated after 16 weeks, the good responders can benefit by the delayed surgical intervention. (10) Very selected cases of low risk oligometastatic patients, can be put under AS, as in Rini's series (11), in which the median time free of systemic treatment was around 14,9 months, with no prejudice in disease progression or deaths. Patients with solitary metastases, in our opinion can have its resection postponed or undergo systemic therapy. Palliative nephrectomy for very symptomatic

patients (e.g. uncontrollable pain, hypertension, hematuria) may rarely be necessary.

Local recurrences

Surgical resection is the better treatment of local recurrences. During SARS-CoV-2 pandemic, we think asymptomatic, small and insidious recurrent lesions can be managed by surveillance until the pandemic end. Symptomatic cases with local complications must be prompted resected. Systemic therapy can be individually discussed, also.

Hereditary RCC

There is no literature regarding hereditary RCC syndromes and COVID-19. We think that majority of these cases can be usually managed, only treating renal lesions ≥ 3.0cm. An exception is the hereditary leiomyomatosis and renal cell carcinoma (HLRCC) an aggressive disease for which immediate surgery is always recommended and systemic drugs are not available and ablatios has not proved efficient (12).

Systemic therapy

The scenario involving RCC patients and the indication of systemic treatment in the course of the COVID-19 pandemic, raises a series of questions that are the focus this discussion. The two main questions that arise are, in the first place, whether patients with RCC really have a higher risk of becoming infected with COVID-19 or not.

Some articles attempt to determine whether patients with cancer are at a higher risk for being infected with COVID-19 and whether they will experience greater morbidity as a result or not. We will briefly focus on two such manuscripts to illustrate how well-meaning attempts at educating the oncologic community must be interpreted with caution.

A nationwide analysis in China demonstrated that, of 1590 COVID-19 cases from 575 hospitals, 18 had a history of cancer (1 vs 0.29% of cancer incidence in the overall Chinese population, respectively), and patients with cancer were observed to have a higher risk of severe events compared with patients without cancer (39 vs 8%; p = 0.0003) (13).

Another study examined a cohort of 1,524 patients with cancer who were hospitalized from December 30, 2019 to February 13, 2020. From this group, 12 patients with cancer were identified with COVID-19 infection (0.79%), compared with 0.37% of individuals who were positive with COVID-19 in the general population of Wuhan during that same time period (14).

These studies assessing susceptibility to COVID-19 infection as well as complications directly related to infection is limited by the small number of patients with cancer in this series of heterogeneous cancer types, and the fact that hospitalized patients with cancer by definition already represent a high-risk population. Besides, without fully controlling the reasons for hospital admission or the potential confounding factors such as non-cancer comorbidities, make it difficult to draw firm conclusions about the risk of COVID-19 infection in these settings.

Articles such as these represent early attempts to assess the impact of COVID-19 on our ability to deliver high-quality cancer care, but these reports are not definitive because of some of the aforementioned limitations. The oncology community is trying to thoughtfully balance fear of COVID-19 against the direct consequences of not treating cancer in an effective or timely manner.

Difficulties in interpreting these data have also been expressed by the Editors of the *Journal of Clinical Oncology*, recognizing that the patients with cancer may indeed be at higher risk for COVID-19 infection and subsequently may experience increased morbidity and mortality compared with similar patients without cancer (15). They also acknowledge that assessing COVID-19 risk is almost certainly more complex than simply having a cancer diagnosis *per se*, and that specific cancers and therapeutic modalities may place some patients at higher risk than others.

The second question that arises from these thoughts is whether systemic renal cancer treatment with tyrosine kinase inhibitors (TKI) or immune checkpoint inhibitors (ICI) increases the risk of infection or worsens the COVID 19. Without considering the risk of exposure to infection from the treatment in itself, or for attending

a health center to get this medication against the recommended social distancing; this type of treatment requires our close attention given the potential consequences of the treatment per se in a yet unknown scenario which has more questions than answers.

We can also see here that the limited cancer patient population described in the first report (13), was curiously characterized by the lack of individuals receiving anticancer immunotherapy. Indeed, only chemotherapy and surgery were cited among treatments received by patients in the month prior to developing COVID-19. Maybe, this could simply be due to the casualty of a small sample, or otherwise, it could suggest that cancer patients receiving immunotherapy are less prone to develop COVID-19 or to be admitted in hospital due to severe coronavirus symptoms. Cancer patients undergoing treatment with anti-PD-1/PD-L1 or anti-CTLA-4 immune checkpoint inhibitors (ICI) currently, constitute a growing population. Their specific susceptibility to bacterial or viral infections has not been investigated. Considering that immunotherapy with ICI is able to restore the cellular immunocompetence, as we previously suggested in the context of influenza infection, the patient undergoing immune checkpoint blockade could be more immunocompetent than cancer patients undergoing chemotherapy (16,17).

There are essentially two main concerns about the utilization of ICI during the COVID-19 outbreak. The first seems to be represented by the potential overlap between the coronavirus-related interstitial pneumonia and the possible pneumological toxicity from anti-PD-1/PD-L1 agents. Even if lung toxicity is not the most frequent adverse event of ICI, it can be life threatening. The overall incidence rate of ICI-related pneumonitis ranges from 2.5–5% with anti-PD-1/PD-L1 monotherapy to 7–10% with anti-CTLA-4/anti-PD-1 combination therapy (18).

The synergy between the two lung injuries, despite only being hypothetical, cannot be surely ruled out. Nevertheless, such an epidemiological coincidence should not prevent the oncologist from offering a potentially effective and often well-tolerated treatment even in the middle of the COVID-19 outbreak, since the duration of the pandemic is still currently unpredictable. This is true in particular considering the potentially curative aim of ICI treatment in the context of highly responsive diseases, such as melanoma and RCC and in the adjuvant setting even more than in the advanced disease.

Considering that underlying lung disease, particularly including interstitial pneumopathy, is considered a risk factor for ICI-related pneumonitis, it could be reasonable taking into account the risk of treating patients while they are developing an initial form of COVID-19.

The second concern seems to be represented by a possible negative interference of ICI in the pathogenesis of COVID-19. Cytokine-release syndrome (CRS) is a phenomenon of immune hyperactivation typically described in the setting of T cell-engaging immunotherapy, including CAR-T cell therapy but also anti-PD-1 agents (19). Considering these aspects, the hypothesis of a synergy between ICI mechanisms and COVID-19 pathogenesis, both contributing to a counter-producing immune hyperactivation, cannot be excluded.

Despite this, we should remember that ICI-induced CRS is a quite rare phenomenon just as that the cytokine storm is not an early event in the COVID-19 pathogenesis, indeed characterizing the late phase of its most severe manifestation, occurring in a minority of patients. It is not likely that cancer patients are still receiving ICI during this phase of the viral illness, we should be focused in delaying treatment for those patients presenting flu-like symptoms at the time of the intended ICI treatment.

Finally, according to the American Society of Clinical Oncology ASCO (20): "At this time, there is no direct evidence to support changing or withholding chemotherapy or immunotherapy in patients with cancer. Therefore, routinely withholding critical anticancer or immunosuppressive therapy is not recommended." No reliable evidence regarding patients with any specific histology therapy (e.g. immunotherapy, tyrosine kinase inhibitors), or subpopulation of patients with cancer (e.g. children, elderly) has been identified.

In this context there are 3 recommendations:

1. There should be a doctor-patient conversation about the balance of potential harms from delaying or interrup-

ting your systemic cancer treatment versus the potential benefits of possibly preventing or delaying COVID-19 infection.
2. That all patients receiving treatment for advanced RCC should take extra precautions to avoid risk of exposure to COVID-19.
3. It may be appropriate to adjust to less frequent dosing intervals when different schedules are considered reasonable options and/or are approved in your jurisdiction for the patient's indication.

Unfortunately, solid scientific data are lacking to guide adjustments to standard-of--care treatment regimens. Whereas sharing and discussing the expert opinions and organization may provide an initial roadmap for proceeding, the oncological community should quickly close key knowledge gaps about the incidence, morbidity and mortality of COVID-19 specific to patients with RCC, to enable evidence-based policies during this pandemic.

DISCUSSION

The care of RCC during the COVID 19 pandemic constitutes a challenge for urologists, oncologists, and all other health professionals evolved. Nowadays there is a reduction of material resources, personal protective equipment, and there is some uncertainty because there is no available specific tests for SARs-CoV-2 for all patients, and when it is available, there are false positives and negatives results, being not possible be totally sure if the asymptomatic patient is really infected or not. Additionally, our older staffs or virus-infected colleagues may require be unavailable by several days, and the younger ones may have to be displaced from their original teams to reinforce frontline pandemic care. As a result, the urology and oncology teams may be reduced, or even stressed (3). Management focused both on patients with CRC and the scarcity of material and human resources is essential, ensuring a safe result for patients without overloading the care system.

As many RCC patients present competing risks for infection and complications of COVID 19, as age >60 years, arterial hypertension, diabetes, overweight, obesity, and smoking, it seems rational to avoid as possible, invasive treatments and repeat hospital visits, that could potentially put them under risk to be exposed to the virus during their treatments. However, there are many kidney cancer patients with aggressive locally advanced tumors, or metastatic cases, who deserve immediate surgical or systemic therapy.

In face of these dilemmas, we must take into account the natural history of heterogeneous clinical presentations of distinct stages of RCC by one side, and by the other side we must act based on the best practices recommended for the treatment of kidney malignance. From these judicious analyses, a risk-based approach must be applied for each clinical scenario, as our proposition above (summarized in Table-1).

We reinforce, that is not possible to warranty the success of all of these suggested approaches, and the environmental conditions can in major or minor grade, prejudice the treatment adherence, patient's follow-up etc. and some cases can progress quickly. Thus, we reinforce our recommendations for the use of a proper informed consent (we did not find in literature references about informed consent for cancer treatment during the COVID 19 endemic). This discussion constitutes personal opinion of authors, since our tertiary center, A.C. Camargo Cancer Center, in Brazil, has developed one informed consent for cancer treatment during this pandemic. All therapeutic choices must be based on shared decisions.

The anecdotal cases of patients unavailable to follow our directrices, or for people refractory to postponement of their treatments, must be considered as exceptions, and they must be solved after extensive discussions regarding the risks and benefits evolved.

Fortunately, actually many new cases of RCC correspond to SRM (21). The acquired experience with studies on AS for SRM, done in elderly people, and the knowledge that the majority of SRM correspond to slow growth lesions, it seems safe to extrapolate its indication, offering AS for all age's patients during the coronavirus era and

Table1 - Summarized risk-based suggested approaches (and alternative options) for renal cell carcinoma during the COVID-19 pandemic.

Stage/clinical presentation	Suggestion (s)	Alternative(s)
cT1aN0M0 (<4.0cm) and complex renal cysts (BosniaK III/IV)	Active Surveillance and postponed SurgeryΨ	Thermal ablation ***Obs.:*** For patients refractory or unavailable for surveillance.
cT1b-T2 N0M0	SurgeryΨ	Surveillance and delayed surgeryΨ (only for selected cT1b and cT2a < 7.0 cm) ***Obs.:*** CT* ou MRI* after 90 days in recommendable) ***Obs.:*** A renal biopsy could be discussed before decision between surgery or surveillance.
≥cT3 and or N+, venous thrombus	Upfront SurgeryΨ	Individualized discussion or tumor board discussion
Low Risk Metastatic	Systemic Therapy (TKI or TKI+ICI) and postponed cytorreductionΨ	Active surveillance for selected cases
Intermediate and poor Risk Metastatic	Systemic Therapy (ICI+ICIC, or ICI+ TKI)	Alternative drugs doses or scheduling intervals between applications. For selected intermediate risks patients with satisfactory response after systemic therapy delayed cytoreductionΨ can be discussed.
Special conditions		
Local Recurrences (small asymptomatic lesion)	Surveillance	Thermal ablation
Local Recurrences (symptomatic or locally invasive lesion)	Wide surgeryΨ	Systemic Therapy and delayed postponed surgery. Individualized discussion or tumor board
Hereditary RCC	Follow usual guidelines (surgeryΨ if >3.0 cm, except for HLRRCC syndrome (prompt resection)	Individualized discussion or tumor board discussion

*CT-Computerized Tomography; ** MR -Magnetic Resonance

All therapeutic decisions must be preceded by a specific informed consent and based on shared decisions. Tumor boards might support decision in difficult cases. Minimally invasive surgeries and early hospital discharge are desirable, even possible. Health professionals must not forget in using their personal protective equipment, perform safe surgery (as for open, as for minimally invasive procedures) (27).

a delayed treatment. For tumors >7.0 cm or local advanced tumors (≥cT3 and or N+ M0), prompt surgery is warranted, since these cases can progress in few weeks. For patients with renal vein, or vena cava thrombus, despite some isolated cases reporting of complete responses with neoadjuvant immunotherapy (22), nowadays the best approach is to perform surgery, except in cases that the tumor and thrombus seems irresectable.

If it is not complicate to postpone the treatment of SMR, and it is also no difficult to indicate immediate surgery to ≥cT3 Any N M0 cases, there is a group of patients in which the therapeutic choice seems more problematic: cT1b, T2a N0

M0. For the majority of these patients, the surgical approach seems more adequate, but we recognize that for some selected pT1b, it is possible to postpone between 60-90 days the surgeries (perhaps an abdominal cross-sectional exam could be done after 90 days), since the growth kinetics of T1b--T2 tumors is similar to SMR (23). A percutaneous biopsy (24), as an exception, could be considered, in some of these patients: if low aggressive histology is reported, the treatment might be postponed. In summary, individualized decisions seem essential for cT1b, T2a (<7.0 cm) N0 M0 cases.

Usually local or locoregional recurrence after radical nephrectomy are managed by RN (25) in face of pandemic, patients with local recurrences, might be evaluated individually: if they present small indolent lesions, we think surveillance could be an option. Conversely, if they present a large, invasive or symptomatic lesions, they could be initially undergo systemic therapy and delayed surgery (personal opinion, evidence is lacking), however some complicated cases (intestinal obstruction, bleeding, or uncontrolled pain, for example, deserves prompt wide resection, with or without intraoperative radiotherapy). Local recurrences after partial nephrectomies can be put under AS, or undergo outpatient thermal ablation, instead prompt surgery (25).

One more dilemma is: what would be the safe trigger for intervention during this pandemic for patients with hereditary RCC? In the literature, the safe trigger for intervention is the lesion size > 3.0 cm (except for HLRCC, which require prompt excision), we do not know if these patients could wait until the same trigger above suggested for sporadic SMR (4.0 cm), with an increased risk of metastatic dissemination; in this way, we recommend to adopt 3.0 cm, and an percutaneous outpatient ablative procedure could be used, instead partial nephrectomy (26).

At the same time that we suggest the use of as minimally invasive surgeries whenever possible, we reiterate that rigorous extra attention should be given to avoid the spreading SARS-CoV-2 through aerosols, that can occurs: during the installation and evacuation of pneumoperitoneum, the use of harmonic scalpels, trocars remove, specimen extraction in laparoscopic and robotic surgeries, or the use of electric scalpel in open surgeries (27). Dedicated surgical rooms and personal protective equipment are absolutely indispensable.

Upfront cytoreduction and/or resection of metastasis for patients with metastatic RCC must be discouraged. We remember that metastatic patients configure a heterogeneous group of patients. For sure, patients with intermediate or poor risks have not benefits with initial surgical approach (9), the use of immunotherapy associated or not with target therapy are largely used (28-30), and must not be postponed for these patients, independently during the SARS-CoV 2 pandemic (29), Salgia et al., (31) suggests the cabozantinib could replace ICI for situations of resource limitations for ICI and for patients with contra-indications (auto immune diseases) for ICI. If we are afraid in using ICI due its potential risks of pneumotoxicity, and CRS, for poor and intermediate risks individuals with RCC during this viral crisis, we could consider to extrapolate the use of this multitarget drug as an option.

Meanwhile, low risk metastatic patients (and some selected intermediate risk ones) can be benefited with upfront cytoreduction; we think at this moment that we can offer two other safe strategies instead the surgery: The first, is to start systemic therapy (TKI or TKI+ICI) and if after late evaluation, they are good responders, (10) we can discuss the cytoreduction. The second option, for selected low risk group might be the AS (11), that beyond do not compromise the outcomes of the patients in an average time around 14 months, also permits the avoidance of side effects of TKY ICI tyrosine-kinase inhibitors or immune check point inhibitors, for patients under risk of COVID-19.

Although it is desirable to reduce the need of hospital visits to get medications and to the side effects of TKI and ICI in this potentially frail population, patients with cancer and COVID 19, present worse outcomes than non-infected oncologic ones (13, 14). Extra concern resides on severe pneumonitis or CRS, for intermediate and poor risk metastatic patients under treatment; however, there is no substitutive safe therapies until this moment. Additionally, there is no certainty when pande-

mic will finish, being temerarious to interrupt or postpone the initiation of systemic therapies for these group of patients, in face of the high risk of progression. Alternative dose scheduling may be discussed, an extra-caution against the viral infection during treatment must be strongly reinforced for patients and they caregivers (20).

Briefly, new studies can clarify the immune repercussions of the SARS-CoV 2 infection concomitant to ICI use: could the immune system become more efficient against the virus or the adverse effects of hyperimmune response could be potentialized?

Although we discussed usual, no usual and exceptions clinical scenarios of RCC in this manuscript, this study presents limitations. It was based on scarce literature regarding RCC and COVID 19 and it is necessary to adapt best usual recommendations for RCC for this pandemic season. Probably, this proposed risk-based recommendations, may be in some grade, influenced be authors' personal biases. For cases not contemplated in this text, for cases of difficult decisions, individualized discussions or tumor board discussion might offer the best approach to be followed.

CONCLUSIONS

During pandemic COVID -19, a tailored stage by stage risk-based approach must be used for a safe management of RCC, aiming to not compromise the oncological outcomes of the patients. Reducing the number of invasive procedures as surgery for indolent and organ-coffined tumors, can minimize risks for RCC population, which due to its characteristics, is usually under risk of infection and complications of COVID 19, and can minimize expositional risks for urologic and oncologic teams, also. On the other hand, patients with aggressive kidney cancer deserve prompt surgical or systemic approach, despite the coronavirus virus risks. There is not enough evidence to avoid systemic therapy for metastatic RCC at this moment. All therapeutic decisions must be preceded by a specific informed consent and based on shared decisions. Tumor boards might support decision in difficult cases. Health professionals must not forget to use their personal protective equipment, perform safe surgery (as for open, as for minimally invasive procedures). More information regarding toxicities of immunotherapy and of target therapy and their implications in this scenario are waited.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Priorities in testis cancer care during Covid-19 Pandemic

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ABSTRACT

Introduction: There is little information on how to prioritize testis cancer (TC) patients' care during COVID-19 pandemic in order to relieve its pressure on the health care systems.
Objective: To describe the recommendations for diagnosis, treatment and follow-up of patients with TC amidst COVID- 19 pandemic.
Material and Methods: Pubmed search and review of the main urological association guidelines on TC.
Results: The biology of TC requires immediate care of patients during diagnosis, initial surgical therapy and management of recurrent disease. Active surveillance is the first choice of management and should be offered to all compliant clinical stage I TC patients provided they understand the need to self-isolate. Active surveillance may also help decrease the demand for intensive care unit beds, ventilators, personal protective equipment, and other critical hospital and human resources by minimizing surgeries without compromising patient outcomes. Complications of therapy and symptomatic patients represent medical emergencies and should be treated immediately. Telemedicine may be useful during follow-up periods.
Conclusions: Most stages of testis cancer require urgent care; however, all recommendations must be adapted to local health care priorities considering that most of these patients are at low risk of severe COVID-19 infection.

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INTRODUCTION

Testicular cancer (TC), although rare, is the commonest, solid-organ cancer in men aged 15 - 44 years. As the tumor is promptly identified and treated, the overall prognosis is excellent even after late diagnosis. While some authors have reported a significant relation between survival and delay in diagnosis, (1, 2) others have shown no impact on survival (3).

Actually, the American Urological Association (AUA), (4) European Association of Urology (EAU) (5) and National Comprehensive Cancer Network (NCCN) (6) guidelines on TC do not make specific considerations in terms of prompt treatment or impact of treatment delay on outcome. Only, the EAU TC guidelines speak about "adequate early treatment" without defining the term "early" (5).

Notwithstanding, it is generally assumed that delays in diagnosis affect the stage of disease at presentation and therefore disease prognosis (7). That is why, all patients suspected of having TC are recommended to be seen urgently (within 2 weeks) by a specialist (8).

The coronavirus disease 2019 (COVID-19) pandemic has created major dilemmas for providers in all areas of health care delivery, including cancer centers, forcing them to make substantial changes. While medical institutions may request that elective surgeries be postponed until the strain on the health care system from COVID-19 has been relieved, the characteristics of elective surgeries in urology oncology are context-dependent and have not been well defined in the current crisis.

Fortunately, TC patients are usually young and healthy. Their risk of severe disease compared favorably with the risk reported in the general population of patients presenting with Covid-19. However, they cannot be excluded from the unprecedented measures taken in health systems worldwide (9).

We herein describe the recommendations for diagnosis, treatment and follow-up of TC patients amidst Covid 19 pandemic based on published studies as well as expert opinion delivered through main urological societies. Needless to say, sound clinical judgment and final decisions should be tailored to the local infection severity and pandemic phase (10).

MATERIAL AND METHODS

We did a Pubmed word search using the terms: "TC and pandemia", TC and covid", "TC and coronavirus" and "urologic surgery and pandemia", and reviewed main urological society guidelines and recommendations in terms of surgical priorities during the COVID-19 pandemic.

Seventy-four manuscripts were retrieved and recommendations from the European Association of Urology and the British Association of Urological surgeons were reviewed.

To facilitate understanding, TC will be approached according to disease stage:

1. Diagnosis
2. TC initial treatment:
3. Management of clinical Stage I (CSI) TC
4. Management of primary metastatic TC
5. Management of residual disease post chemotherapy.

Follow-up

Unfortunately, there might not be high-quality evidence for the compromises proposed but it is anticipated the new information will function as an additional guide to the management of urological conditions during the current COVID-19 pandemic.

RESULTS

The EAU categorized recommendations with increasing degrees of priorities as follows (11):

- LOW PRIORITY: Clinical harm (progression, metastasis, loss of function) very unlikely if postponed 6 months.
- INTERMEDIATE PRIORITY: Cancel but reconsider in case of increase in capacity (not recommended postponing more than 3 months: Clinical harm (progression, metastasis, loss of organ function) possible if postponed 3-4 months but unlikely.
- HIGH PRIORITY: The last to cancel, prevent delay of > 6 weeks. Clinical harm (progression, metastasis, loss of organ function and deaths) very likely if postponed > 6 weeks.
- EMERGENCY: Cannot be postponed for more 24 hours. Life-threatening situation.

TC diagnosis:

All patients with suspicion of TC should undergo a bilateral testicular ultrasound within 24 hours of clinical examination, which should include physical examination of supraclavicular, cervical, axillary and inguinal lymph nodes, breasts and testicles.

Like normally done outside any pandemic state, serum tumor markers should be evaluated before and after orchiectomy.

Non contrast-enhanced CT scan of the chest and contrast-enhanced CT scan of the abdomen and pelvis should be done in patients with

a diagnosis of TC ideally before orchidectomy. In case of iodine allergy or other limiting factors perform MRI of the abdomen and pelvis. According to the EAU recommendations, if diagnostic imaging studies had not been performed before orchidectomy, they may be postponed awaiting pathology result but no more than 7 days.

TC initial treatment:

Radical orchiectomy should be performed as soon as possible because it is an outpatient procedure and will guide further treatment (12). EAU experts consider orchidectomy a surgical emergency, however, it may be postponed 2-3 days, as well as the pathological examination of the testis. Histologic evaluation time may vary significantly from institution to institution and health care systems (private, public, etc.).

MRI of the brain (or brain CT if not available) should be indicated on an emergency basis in patients with central nervous system symptoms, multiple lung metastases, high β-hCG values, or those in the poor-prognosis IGCCCG risk group. MRI of the brain could eventually be postponed until chest CT or marker results are available, but then becomes an emergency.

Patients at high-risk for contralateral germ cell neoplasia in situ are recommended to undergo biopsy of the contralateral testis during orchidectomy. They include patients with an atrophic contralateral testis (< 20 cc volume on ultrasound) who present before the age of 31 years, (13) azoospermic (14) and present ultrasonographic abnormalities. (15, 16) If contralateral biopsy was not done during contralateral orchiectomy, it can be postponed 6 months.

Sperm banking is another low priority procedure, particularly in those patients who had not done it prior to orchiectomy and do not need adjuvant chemotherapy or radiotherapy. In patients scheduled for adjuvant treatment sperm banking becomes an emergency and should be done prior to starting treatment.

There is currently no evidence of vertical transmission of COVID-19. However, patients may be offered testing at their discretion at the time of performing standard serology (i.e. HIV/Hepatitis testing) prior to sperm cryopreservation if specific covid-19 diagnostic tests are available.

Management of clinical Stage I (CSI) TC

Active surveillance is the first choice of management in compliant CSI TC patients, particularly during COVID-19 pandemic. Active surveillance should be offered to all these patients with seminoma and low risk (no lymphovascular invasion) non seminoma germ cell tumors (NSGCT) provided they understand the need to self-isolate (10).

Unless the patient has contraindications to other forms of therapy, RPLND should be discouraged in order to eventually avoid use of an intensive care unit bed or a ventilator machine, and decrease patient length of hospital stay, thus, decreasing his chances of becoming Covid-19 infected.

CSI seminoma or NSGCT patients not accepting active surveillance need to be treated. They are considered high priority and should be treated within 6 weeks of histologic confirmation (High priority). This group of patients with CSI seminoma should be treated with one course of carboplatin at AUC7. Experts agree that in spite of the lack of evidence on the association of bleomycin with severe lung COVID disease, bleomycin should be avoided when possible and hematopoietic growth factors (G-CSF) should be co-administered to diminish the incidence of neutropenia and infection in all patients with germ cell tumor (GCT) receiving chemotherapy.

Patients with low-risk NSGCT CSI not willing or unsuitable to undergo active surveillance should receive one cycle of BEP and G-CSF. Patients with high risk CSI-NSCGT (presence of lymphovascular invasion) should be treated with one course of BEP and G-CSF if they are not willing to accept AS.

Primary nerve-sparing RPLND should only be indicated in CSI -NSGCT patients with contraindication to adjuvant chemotherapy and unwilling to accept active surveillance, or in those with teratoma with somatic-type malignancy.

Management of primary metastatic TC

Except for patients with clinical stage IIA seminoma who can be treated with either radiotherapy or chemotherapy within 6 weeks of histologic confirmation, all other patients with me-

tastatic disease at presentation should be treated immediately.

Patients in a good general condition may delay the initiation of chemotherapy for 7 days. In addition, short planned delays in chemotherapy for good-risk GCT patients (≤7 days per cycle) also appear to be acceptable since they may prevent serious toxicity in this curable patient population (17).

Clinical stage IIB seminoma patients should be treated with chemotherapy according to the International Germ Cell Consensus Classification (IGCCC) good risk group. (3x BEP o 4x EP + G-CSF) (18,19) Radiotherapy may be considered as alternative in selected clinical stage IIB seminoma depending on availability.

Patients with stage ≥ IIC seminoma should receive primary chemotherapy based on the same principles used for NSGCT. IGCCC good risk NSGCT should be treated with 3x BEP o 4x EP + G-CSF while the recommended therapy for IGCCC intermediate or poor risk groups is 4x VIP or 4x BEP + G-CSF. (6) Carneiro et al. recommend the use of VIP (Etoposide; Ifosfamide and Cisplatin) in patients with intermediate or poor risk metastatic GCT, instead of the 4x BEP, to avoid the use of bleomycin (12). Again, patients in a good general condition may delay the initiation of treatment for 7 days.

In a life-threatening situation due to extensive metastasis, patients should be hospitalized and commence chemotherapy prior to orchidectomy (clinical principle).

Management of residual disease post chemotherapy

Post-chemotherapy full bilateral RPLND of either residual masses after chemotherapy for NSGCT with negative serum levels of tumor markers or growing teratoma are considered high priority and the surgery should be performed within 6 weeks of completed chemotherapy.

Follow-up of TC

Patients with Seminoma and NSGCT CSI on AS or after adjuvant chemotherapy are recommended to be followed within 6 weeks of the original appointment (High priority). EAU experts recommend not to postpone follow-up beyond 3 to 6 months of the original appointment in patients with metastatic disease after adjuvant treatment or complete remission.

Direct-to-consumer (or on-demand) telemedicine may allow patients to be efficiently followed, as it is both patient-centered and conducive to self-quarantine, and it protects patients, clinicians, and the community from exposure. It can allow physicians and patients to communicate any time as needed, using smartphones or webcam-enabled computers (20).

Patients with symptomatic brain metastases following treatment, post-obstructive polyuria or symptomatic postoperative complications (infection, bleeding, lymphoceles/ lymphatic ascitis, etc.), intractable pain or symptomatic neutropenia during or after chemotherapy (fever, sepsis) represent medical emergencies and should be treated immediately.

DISCUSSION

Urologists can make a substantial contribution to the health care systems by decreasing the demand for hospital beds, ventilators, personal protective equipment, and other critical hospital and human resources by minimizing surgeries without compromising patient outcomes whenever possible (21).

Medical specialists in general and urologists in particular are encouraged to weigh the impact of nonsurgical therapies such as systemic chemotherapy (that can leave patients at greater risk of contracting and potentially succumbing to COVID-19) and surgical risks against the natural history of the disease in case it is not timely treated.

Generally speaking, considerations should include nonsurgical treatments whenever available or deferral of surgery until patient risks of in-hospital COVID-19 infection, demand for ventilators and inpatient beds diminish. The recommendation for different stages of disease in patients with testis cancer are summarizes in the Table-1.

The impact of surgical wait time on the outcome of testis tumors remains controversial. (22-24) There are few studies evaluating components

of wait times (e.g. delay in diagnosis, delay in orchiectomy) in TC patients; however, differences in study data availability, method of analysis and wait time definitions precluded statistical pooling of the findings (23). Nonetheless, given the unpredictable biology and speed of TC cell dissemination, both diagnostic and treatment delays are strongly discouraged (17).

Regarding treatment options in patients with low volume stage II seminomas (IIA and IIB), some authors recommend radiotherapy to avoid the use of chemotherapy (12). However, several radiotherapy centers are currently closed due to the COVID-19 pandemic.

The same authors also recommend 4 cycles of VIP (Etoposide 75mg/m2 IV on Days

Table 1 - Summary of recommendation for different stages of disease in patients with testis cancer.

1- Diagnosis:

- Low priority: Sperm banking
- Emergency: Ultrasound, physical exam and serum tumor markers

2- Initial treatment:

-Low priority: Contralateral biopsy (see text)

- Emergency:

- Orchiectomy with 2 -3 days
- Imaging within 7 days in asymptomatic patients

3- Stage 1 management:

- Low priority: In case AS is offered according to guidelines
- High priority: In case treatment is offered according to guidelines

4- Treatment metastatic disease:

- High priority:

- Any adjuvant treatment in stage IIA Seminoma (Radio or chemotherapy)
- Adjuvant treatment in stage IIA/B NSGCT with negative markers

- Emergency:

- Treatment in stage $\geq$ IIB Seminoma and NSGCT within 7 days (Chemotherapy)
- Symptomatic, life threatening or poor risk

5- Management of residual disease post chemotherapy

- Low to high priority: Can be delayed from 6 weeks to 6 months depending case by case (telemedicine)

- Emergency:

- Symptomatic postoperative complications, pain, neutropenia with fever o sepsis, etc.

1-5; Ifosfamide 1200mg/m2 IV on Days 1-5 with same protection and Cisplatin 20mg/m2 IV on Days 1-5, every 21 days) in patients with intermediate or poor risk metastatic GCT, instead of the 4x BEP, to avoid the use of bleomycin. Although there is no evidence on the association of bleomycin with severe lung COVID disease, it is generally agreed to avoid bleomycin when possible. Hematopoietic growth colony stimulating factors (G-CSF) are recommended in all patients with germ cell tumor (GCT) receiving chemotherapy to diminish the incidence of neutropenia and infection (11, 12).

Disasters and pandemics pose unique challenges to health care delivery and the multiple potential benefits of telemedicine are not new (25). More than 50 U.S. health systems already have telehealth programs to allow clinicians to see patients who are at home. However, it is not widely utilized in other parts of the World. Telemedicine visits can be conducted with both patient and clinician at home, greatly limiting travel and exposure and permitting uninterrupted care of patients (20). Telemedicine is an attractive strategy to follow CSI patients on active surveillance as long as they can periodically provide imaging studies and serum tumor markers results. Some of telemedicine limitations include cost, training, reimbursement, credentialing and impossibility to perform physical exam, which is extremely important during active surveillance.

Needless to say, all recommendations are mindful of significant differences between countries and regions. Depending on resources, doctors will need to make decisions according to local health care priorities. Countries or even provinces that have not had high rates of death from COVID-19 could consider similar approaches that involve balancing pandemic control with providing continued cancer care (26).

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Therapeutic and Surgical Indications for Patients with Penile Cancer in the COVID-19 era

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ABSTRACT

Purpose: The aim of this work is to review and synthesize the existing evidence and recommendations regarding to the therapeutic and surgical indications as well as monitoring of patients with Penile Cancer in COVID-19 era and to propose an action protocol to facilitate decision-making.
Material and Methods: A non-systematic review of the literature regarding the management of penile cancer during the COVID-19 pandemic was performed until April 30, 2020. We propose our recommendations based on this evidence.
Results: Penile cancer is an uncommon but aggressive disease. Prognosis is determined by several characteristics, being the most important the presence of lymph nodes, in which case, treatment should not be delayed. For these reasons, an initial evaluation is mandatory. Priority classifications, based on the oncological outcomes when treatment is delayed, have been made in order to separate deferrable disease from the one that needs high priority treatment. In penile cancer with low risk of progression, surgical treatment can be delayed, but other options must be considered, like topical treatment or laser therapy. In cases with intermediate risk of progression, surgical treatment may be delayed up to three months, but we must consider radiation therapy and brachytherapy as effective options. When feasible, follow-up should by telemonitoring.
Conclusions: In the COVID 19 era, initial evaluation of the patient is mandatory. Histological diagnosis with local staging is necessary before offering any therapeutic option. In case of superficial non-invasive disease, topical treatment is effective in absence of lymph node involvement. In selected patients, radiotherapy is an organ-preserving approach with good results. Non-deferrable surgical treatment must be performed by an experienced surgeon and as an outpatient procedure when possible. When indicated, iLND should not be delayed since it is decisive for patient survival. Follow-up should be by telemonitoring.

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INTRODUCTION

Penile cancer is an uncommon pathology, with an overall incidence, in industrialized countries, of around 1/100.000 males in Europe and USA (1). The incidence is affected by race and ethnicity, with the highest incidence in white Hispanics, followed by Alaskans and native American Indians. In other parts of the World, such as South America, South East Asia and parts of Africa, the incidence is much higher (2). Several risk factors have been identified, such as HVP infections,

smoking, phimosis, chronic penile inflammation and multiple sexual partners (3, 4).

Winters et al. made an analysis of the United States national cancer database from 1998 to 2012, describing that the presence of pathological subtype of the disease, perineural and lymphovascular invasion, depth of the invasion and grade in the primary tumor will determine the prognosis (5).

When analyzing the social characteristics of the patients, Jimenez Ríos et al. described that low socioeconomic status, poor education and delay in seeking medical attention are related with advanced disease. This analysis was made in Mexico and concluded that a delay of 10 months between the appearance of the first symptoms and the patient seeking for medical attention was related with advanced disease and worse prognosis (6).

On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic (7). This has led to dramatically changes on medical and surgical priorities. Postponement for all outpatient and elective activities to save facilities and resources for urgent cases and COVID-19 patients have been adopted by most hospitals in the affected countries. We know that cancer patients are characterized by their higher susceptibility to infectious diseases compared to general population with 3.5 folds increased risk of COVID-19 related serious events (8). Therefore, the choice of urgent and emergent surgeries that should still occur will depend on the capacity and demand, but also must be counterbalanced by the effects of delaying surgeries (9). As COVID-19 continues to spread, governments have imposed increasingly aggressive measures that have demonstrated benefits in reducing the spread of the virus minimizing the impact that cases have on local health care systems (7). This is generating a rapid and tragic health emergency worldwide, due to the need to provide assistance to an overwhelming number of infected patients and, at the same time, treat all the non-deferrable oncological and benign conditions (10).

Liang W et al. in a nationwide analysis of cancer patients with COVID-19 infection proposed that intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer should be considered in endemic areas (11).

Later, Xia Y et al. reported that these findings can´t be generalizable due to the small sample analyzed, the heterogeneity on the type of cancers, the great difference in the course of the disease and the different treatment strategies. (12) Uncareful delay of onco-urologic surgeries may have an impact on short-term progression and/or mortality (8).

Knowing that penile cancer is an uncommon, but yet aggressive disease, there is a need to have easy to follow strategies and protocols for early diagnosis, adequate treatment and follow up during COVID-19 pandemic.

MATERIAL AND METHODS

A non-systematic review of the available literature on the management of penile cancer during the COVID-19 pandemic was performed. We navigated through Pubmed, Cochrane library, the American Urology Confederation (CAU) library of COVID-19, we reviewed the European Urology Association (EUA) Rapid Reaction Group recommendations, the British Association of Urological Surgeons (BAUS) recommendations, the National Comprehensive Cancer Network (NCCN) guidelines and the American Urology Association (AUA) COVID-19 library in search of literature available in English and Spanish until April 30, 2020.

We described and analyzed the different protocols and recommendations proposed by different authors and scientific organizations, and based on this evidence and our experience, we created an action protocol for early and safe diagnosis, adequate treatment and follow up of patients with penile cancer during COVID-19 pandemic.

RESULTS

COVID-19 pandemic has led to dramatically changes on medical and surgical priorities. Postponement for all outpatient and elective activities to save facilities and resources for urgent cases and COVID-19 patients have been adopted by most hospitals in the affected countries (8). This is a problem that is affecting health services worldwide.

Naspro and Da Pozzo stated that the real challenge in this time, is that the health service in Italy is currently unable to easily deal with other conditions except treatment of COVID-19. Urologists manage patients with oncological diseases and surgical priorities, as well as non-oncological conditions that can affect quality of life. Regional guidelines require that any patient requiring oncological surgery must be treated within 30 days from diagnosis. Departments struggle to meet this deadline normally, now it´s even harder (13).

Pulliati et al.(8) in a review of the literature available of COVID-19 and Urology, quotes the work of Liang et al. (11), who stated that cancer patients are characterized by their higher susceptibility to infectious disease compared to general population with 3.5 folds increased risk of COVID-19 related serious events in the form of intensive care admission, requirement for mechanical ventilation, or death due to their immune compromised state related to the nature of their malignancy and the anti-cancer management (chemotherapy, radiotherapy, or surgery). This paper recommends to delay all elective cancer surgeries or adjuvant chemotherapy in patients with stable cancer. Wang et al. (14) reported that the major risk factor for cancer patients during COVID-19 pandemic is the inability to receive sufficient medical support.

Xia Y et al. (12) reported that Liang et al. (11) findings are not generalizable due to the small sample analyzed, the heterogeneity on the type of cancers, differences in their course and the different treatment strategies.

In this same line, Méjean A. et al. as part of the Cancerology Committee of the French Association of Urology (CCAFU) published expert opinion recommendations based on literature review for cancer treatment (15). They stated that a 3-month delay in diagnose and treatment of penile cancer decreases the possibility of conservative treatment. This 3-month delay seems to have no impact in 5-year overall survival or recurrence free survival. After 6-month delay, survival reduces after 2 years. A 3-month delay in the treatment of lymph nodes, significantly decreases 5-year specific survival (39.5% when compared with 64.1% when there is no delay). This idea reinforces the statement of Xia et al. that we cannot treat all patients and all pathologies as a same (12).

We know that prognosis is determined by the pathological subtype of the disease. In this case, the verrucous subtype is considered to demonstrate low malignant potential, while adenosquamous and sarcomatoid variants carry a worse prognosis. The presence of perineural and lymphovascular invasion, depth of the invasion and grade in the primary tumor are also relevant in determining prognosis (2, 16).

This is the reason why, potential new penile cancers require clinical assessment, as stated by the British Association of Urological Surgeons (BAUS) (17), in order to determine the most appropriate treatment. It is vital to perform a good physical evaluation of the penile lesion (s) with all its characteristics (diameter, location, number, morphology and involvement of other structures) as well as the presence of suspicious lymph nodes. To complete this initial evaluation, histologic diagnosis with punch, incisional or excisional biopsy is paramount in determining the treatment algorithm (2, 16).

Once histological diagnosis has been made, standard treatment for superficial non-invasive lesions; Tis or Ta should be with penis-preserving techniques including topical treatments, laser therapy, Mohs surgery and conservative penile surgery. In T1G1-2 disease, careful consideration should be given for penile-preserving techniques if the patient is reliable in terms of complications with close follow-up. This includes wide local excision, glansectomy in selected cases, Mohs surgery, laser therapy and radiation therapy. In T1G3 or ≥T2 extensive surgery, RT and in some cases, brachytherapy may be feasible (2, 16).

The presence and extent of regional inguinal lymph node metastases have been identified as the single most important prognostic indicator in determining long-term survival (16).

During COVID-19 pandemic, there´s a need to create easy to follow recommendations and protocols that are adapted to the actual health situation in order to guarantee a safety environment for the patient and medical staff. That´s why different associations, expert groups and authors are doing great efforts to review available data and provide adapted strategies.

There´s a need to classify oncological diseases in groups according to their clinical stage, and state priorities for treatment.

The European Urology Association (2), through the guidelines office, proposed a rapid reaction group (GORRG) on 19th March 2020, to facilitate the development of adapted guidelines to deal with a range of situations and priorities. Levels of prioritization were established taking in count the impact of delay on primary outcomes, possibility of alternative methods that could replace the standard procedure with less operating room requirements, presence of co-morbidities and/or increased risk of complications among others. Low priority was used to classify diseases that were very unlikely to cause clinical harm if postponed 6 months. Intermediate priority for diseases that can cause clinical harm if postponed 3-4 months even though it´s unlikely. High priority when disease can cause clinical harm if postponed more than 6 weeks, and emergency for life threatening situations. A similar classification was made by Ficarra V. et al. who distinguished urological procedures to treat cancer in four categories: a) Non deferrable, b) Semi-non-deferrable, c) Deferrable, d) Replaceable by another treatment (10).

Goldman et al. from Cleveland Clinic urology department made a tier system from 0-4 to help prioritize surgical procedures. In this classification they used five priority tiers, where 0 is considered an emergency, and 4 a non-essential surgery that can be delayed for long time. Penile cancer is listed a priority 1 in this tier classification. This classification was based on the available data regarding risk of progression but mostly from expert opinion (18).

In this case we made our classification (Table-1) based on the classification system proposed by Ficarra V. et al. which is similar as the proposed by the EUA (2), because it allows us to stratify one same disease in a different category depending on its clinical stage. The time of delay in deferrable disease will be 6 months and in semi non-deferrable 3 months (10).

The presence of inguinal lymph nodes will automatically classify the disease as non-deferrable. In semi-deferrable disease, the possibility to access priority medical assistance or telemonitoring should be available. During this time, the patient must perform self-examination and in case of noticing palpable inguinal lymph nodes, medical attention should be a priority.

In this case, in order to complete diagnosis, chest, abdomen and pelvic CT scan should be performed (2, 16, 19).

In a literature review made by Wallis C. et al. they describe that patients who receive early inguinal lymphadenectomy; with median

Table 1 - Treatment priority classification for Penile Cance during COVID-19 pandemic

Penile Cancer Priority Category	Non-Deferrable	Semi non - Deferrable	Deferrable	Emergency
	(6 weeks)	(up to 3 months)	(6 months)	
Definition	≥ T1G3, any N+	T1G1, T1G2 (non verrucous)	Tis, Ta and some T1G1	Life-threatening situations, opiod-depending pain, urinary flow obstruction.

Adapted from Ficarra et al. and the EUA GORRG recommendations (2, 10)

time to surgery of 1.7 months, range 0-6 months, had significantly lower five-year cancer specific mortality than those who underwent delayed intervention (20).

In deferrable disease, when other treatment options are available, they must be offered.

Méjean A. et al. (15) proposed that when all therapeutic options are available and low risk disease is being treated; Tis (PeIN), topical treatment should be the first option. In case of conservative treatment failure, if strict supervision is available (this may be done by telemonitoring), reasonable delay on surgery may be an option, and, when invasive disease; <T1G2 or verrucous cancer, with low risk of lymph node affection, a delay on surgery must be discussed with the need of lymph node evaluation. Alchiede Simonato et al. (19) made a simplification of the diagnostic therapeutic algorithms based on the EUA guidelines and the experience gained in Italy during this crisis. They proposed that, when indicated, penectomy with inguinal lymph node dissection must not be delayed. We understand that this refers to patients with ≥T1G3, or any N+. This was also stated by Puliati et al. (8).

Following the same line, Stensland et al. (9), suggested a triage for surgical cancer treatments, where they recommend to not delay treatment of possible clinically invasive penile cancer or obstructive cancers. Prevention of lymph node metastases is vital to spare significant patient morbidity.

They emphasized the importance of performing surgery as an outpatient procedure when feasible.

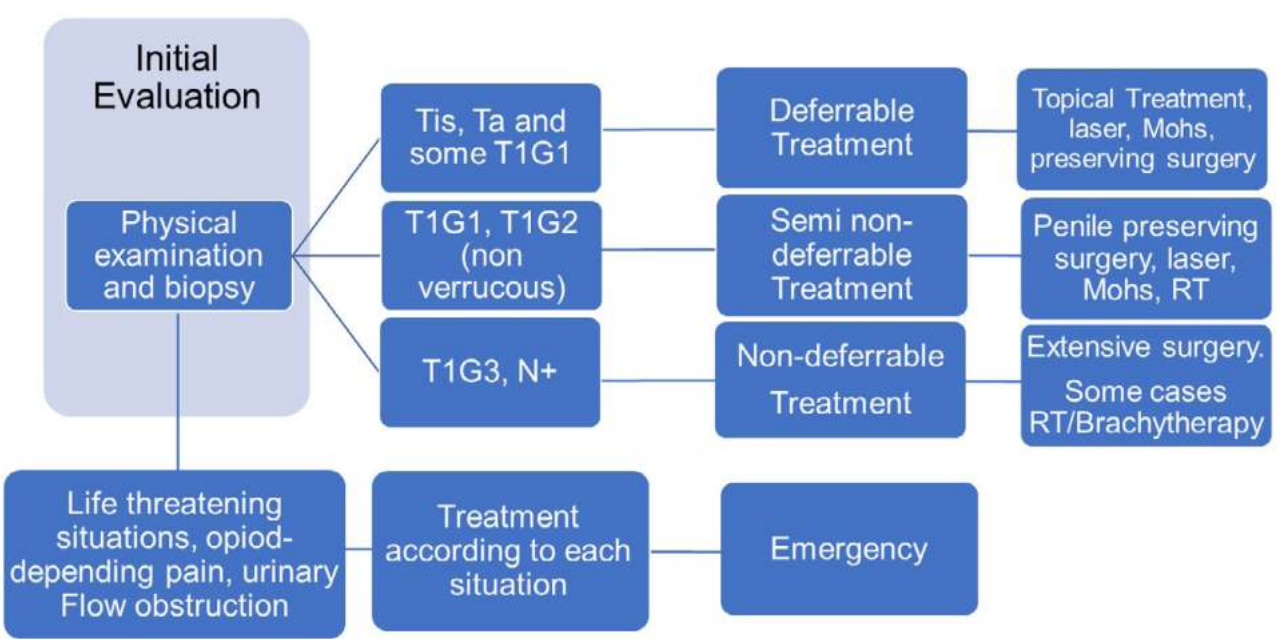
In order to facilitate decision-making for treating penile cancer during COVID Era, we created a recommendation flowchart (Figure-1).

Simonato A. et al. (19), the EUA protocol created by the GORRG (2) and the BAUS recommendations (17) all coincide that follow-up should be by remote monitoring.

DISCUSSION

We made a review of the literature available at the moment, for the diagnosis, treatment and follow-up of penile cancer during COVID-19 pandemic. Despite the lack of information at this

Figure 1 - Decision-making recommendations for Penile Cancer during COVID-19 era.



point, several authors and scientific organizations are moving quickly to make different protocols and guides of recommendations to facilitate decision--making in urological cancer disease during the COVID-19 pandemic.

Based on the characteristics of penile cancer; epidemiological, histological and clinical behavior, we know we are dealing with an uncommon but aggressive disease, with high mortality when diagnosis and treatment are delayed. During COVID-19 pandemic hospitals worldwide have been forced to make changes in order to save facilities and resources for urgent cases. This has led to postponement of outpatient and elective activities.

As more information appears, protocols are being adapted. Liang et al. (11) recommended to delay all elective cancer surgeries or adjuvant chemotherapy in patients with stable cancer. This was based on the premise that oncological patients have higher susceptibility to infectious diseases. It´s well known that evolution, treatment response and prognosis vary between different cancer diseases, so we must treat each one individually, as reported by Xia et al. (12) and Wang et al. (14).

Different classifications have been made in an attempt to establish levels of prioritization. The EAU guidelines (2), Ficarra et al. (10), Méjean et al. (15), the BAUS guidelines (17) and Goldman et al. (18) agree that different cancer diseases can be classified in low priority (deferrable), intermediate priority (semi non-deferrable), high priority (non-deferrable) and emergencies, depending on the probable oncological outcome if attention is delayed. In terms of treatment the EAU guidelines (2), Stensland et al. (9), Ficarra V. et al. (10), Méjean et al. (15), the NCCN Guidelines (16), Simonato (19) and Wallis (20) all recommend special attention to the presence of inguinal lymph nodes because they will affect prognosis. In case of affection, treatment must not be delayed.

During COVID-19 pandemic, authors agree that, when feasible, follow-up can be done by remote monitoring, phone calls or even by sending pictures (2, 17, 19).

CONCLUSIONS

In the COVID era, evaluation of the patient is necessary in order to clinically determine the stage of the disease and proceed to adequate treatment. Appropriate safety measures must be taken to guarantee the safety of the patient and medical staff. Histological diagnosis with local staging must be obtained before offering a therapeutic option. In case of superficial non-invasive disease, topical treatment is effective and should be the first option in absence of lymph node involvement. In selected patients with T1-2 lesions <4cms in diameter, radiotherapy is an organ-preserving approach with good results. It can be given as external radiotherapy combined with brachytherapy boost or as brachytherapy alone.

When surgical treatment can´t be delayed, it should be performed by an experienced surgeon, under appropriate safety measures and as an outpatient procedure when feasible. When indicated, LND should not be delayed since it is decisive for patient survival. The follow up should be performed by telemonitoring when possible.

ABREVIATIONS

CAU = American Urology Confederation
EAU = European Urology Association
GORRG = Guidelines Office Comissioned a Rapid Reaction Group
NCCN = National Comprehensive Cancer Network
BAUS = British Association of Urological Surgeons

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Impact of COVID-19 in Female Urology

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ABSTRACT

This review discusses the impact of COVID-19 in Female Urology, revises the most important disorders in this field and how their diagnosis and treatment may be modified due to the current pandemic. The text also discusses new options such as telemedicine and what clinical situations within Female Urology should be of utmost importance for the urologist to be careful about. We also discuss how surgeries are being postponed are resumed according to the local scenario.

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2) is a pandemic disease that has contaminated nearly 4 million habitants worldwide and caused almost 300,000 deaths. It is a single-stranded RNA virus, with high infectivity rate, and although most of patients recover from disease, less than 20% of cases may worsen and need intensive care units for ventilatory support. Transmission occurs mainly by inhalation of droplets and aerosol containing the virus, but also through mouth, nose and eyes contact. Fecal-oral transmission may be possible. Laboratorial diagnosis can be done by RT-PCR (reverse transcriptase-polymerase chain reaction) and IgM/IgG antibody immunoassays, imaging is basically investigated by thoracic computerized tomography, and treatment is still controversial (1).

In summary, the pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) had a great impact not only for

medical management, but also in doctor-patient relationship and for health care providers (2). Moreover, our patients present many known risk factors for COVID-19 (age over 60 years, hypertension, diabetes, etc) so their protection is essential.

REPERCUSSION ON FEMALE UROLOGY

As female urology deals mostly with procedures related to quality of life, most of the these can be postponed. Telemedicine is an important tool, irrespective of whether the institution has a proper platform or if the doctor uses mobile applications and smartphones (3).

In Latin America, doctors will face many barriers such as: lack of massive testing for patients, , disparities between the number of COVID-19 patients admitted to public intensive care units (ICUs) versus private ICUs, under notification of data regarding infection and death rates and not enough personal protective equipment (PPE) (4).

Testing should be massively encouraged prior to surgery as well as revision of symptoms regarding COVID-19 with the patient. Within the operating room, N-95/FFP3 masks should be guaranteed for the surgical team (as well as the rest of accessories – shoe covers, gown, protective head covering, gloves and eye protection), a small number of people should be inside the operating room, and negotiation/discussion with the anesthesia team should be done prior to each procedure. For vaginal and abdominal surgeries, use of N-95 masks plus face shields should be present and smoke dispersion should be avoided as much as possible. In relation to laparoscopic procedures, discussion about pros and cons versus laparotomy should be done with the entire team, and extreme care should be taken to reduce pneumoperitoneum escape. Until time of writing, no data were available proving that COVID-19 viral particles were identified in surgical smoke (5).

MANAGEMENT

In general, most urogynecological disorders can be treated conservatively (3). Data comparing telephone versus presential outpatient visit for postoperative floor disorders is already available (6). The most important disorders that lead patients to seek medical attention are mainly (7):

1 - Urinary tract Infection (UTI)
2 - Urinary incontinence (UI)
3 - Pelvic Organ Prolapse (POP)

We shall also discuss about common procedures in urogynecology, such as urodynamics and cystoscopy. Table-1 comprises the complications potentially related to these disorders that may request an emergent visit to the hospital.

Urinary tract infection (UTI)

Women with UTI symptoms should initially be managed by remote communication. The most prevalent and predictive symptoms are dysuria, worsening frequency or urgency, gross hematuria (8). Presence of vaginal symptoms reduces the predictive value for UTI. In a grossly scenario, clinical history allows the female urologist to separate the complicated presentation from non-complicated UTI.

Acute bacterial cystitis should be managed empirically as we will not have access, in many facilities, to guided-antibiograms. Empiric treatments with either trimethoprim-sulfamethoxazole (TMP-SMZ) or nitrofurantoin are cost-effective choices. Some options for uncomplicated UTI are TMP-SMZ 160/800 mg orally twice for three days (if local antibiotic resistance rate is not exceeding 20%), nitrofurantoin 100 mg orally twice daily for 5 days or fosfomycin trometamol 3 g once. If the patient does not improve or diagnosis in unclear to be considered by telemedicine, a urine sample may be left at the clinic for urinalysis, and if positive, a sample may be sent for culture and sensitivity (3).

Urinary incontinence (UI)

For initial appointments, telemedicine allows history-taking. One day prior to consultation, the short-form questionnaires may be sent by email to improve consultation, or patient may answer the questionnaire guided by a nurse or chaperone prior to consultation at the same day. We must consider the normal scenario of an outpatient clinic; thus, in general, UI will be probably divided into stress, urgency and mixed. Other forms will probably require a presential visit. In

Table 1 - Complications from main disorders in Female Urology that may demand a visit during COVID-19 pandemic.

Complications	Subtypes	Treatment*
Urinary tract infection	Relapsing UTI	Change antibiotics after requesting an urineculture
	Complicated UTI	Hospitalar management if patient present clinical instability with antibiotics and/or surgery
	Acute pelvic pain with urinary symptoms	Endovenous analgesics plus screening for differential diagnosis
Urinary incontinence	Postoperative acute retention	Clarify reasons and initiate treatment: sling mesh loosening or transurethral catheterization
	Postoperative urogenital fistula	Transurethral catheterization, prophylactic antibiotics and schedule surgery after pandemic
Pelvic organ prolapse	Bleeding or pain secondary to vaginal pessary	Pessary removal with or without sedation
	Vaginal vault rupture after POP surgery	Surgical vaginal vault closure
	Bladder eversion	Manual reduction with or without surgical management

* If surgical treatment, preoperative recommendation would be to test all patients if COVID-19 kits available, or to prioritize oligosymptomatic or symptomatic patients. Postoperative recommendation would be for same-day discharge and to consider prophylaxis or treatment of anticoagulation for symptomatic COVID-19 cases.

mixed urinary incontinence, direct treatment towards the predominant symptom.

Conservative therapy is the first line therapy, and the alignment with a physical therapy improves resolution of each case. Pelvic floor muscle exercises, Kegel exercises, timing voiding should be mainly conducted on-line. At present there are many apps like iPelvis and others that allow for home practicing.

Secondary referral must be considered for some specific symptoms such as: gross hematuria, persistent bladder or urethral pain, previous continence surgery with pain and/or recurrent UT and voiding difficulties, including urinary retention.

Two COVID-19 symptoms may merge or cause confusion in differential diagnosis – dry cough with no underlying cause (pulmonary baseline disorder) and diarrhea – if patients start to present these symptoms, associated with fever, local testing should be provided.

Patients with severe urgency may be managed with antimuscarinics or beta 3 adrenergics. It is important to explain the side effects, success rate and the need for adhesion, which is typically low. Oxybutinin should be avoided in the elderly, antimuscarinics should be excluded for disorders such as closed-angle glaucoma. Patients should be aware that any major side effect should make them

contact the hospital for referral and/or further instructions. One side effect (SE) from solifenacin is QT prolongation during electrocardiogram. Thus, for a patient with COVID-19 symptoms treated in an institution that might consider using drugs such as chloroquine, this must be discussed with the physician prior to initiating treatment. If patient needs to be referred to a hospital, she should carry a copy of her prescription.

Pelvic organ prolapse (POP)

Patients with POP should initially be managed by remote communication. Specific questionnaires are available, and it is important to calm the patient regarding the evolution of POP. Most of the cases do not present POP worsening in 9-12 months of follow-up (9).

Facilities for virtual communication can vary and include telephone/ video conferencing. If prolapse is mild, patient should be advised to perform pelvic floor muscle training since there is no strong evidence that it can reduce POP, it may increase pelvic consciousness (10). On the other hand, if there is a large bulge affecting bladder and bowel emptying and/or in presence of ulceration, a face-to-face appointment will be required. Follow-up of surgical procedures can be carried out virtually using telephone or video conferencing with questionnaires focusing on patient reported outcomes (satisfaction, subjective improvement) but if a reason to see patient is identified, a face-to-face appointment may be the only option. If so, recommended PPE should be worn. In rare circumstances, POP may complicate as rupture of vaginal vault prolapse (Figure-1) or bladder eversion and surgery is recommended immediately.

Urodynamics and cystoscopy (Figure-2) are common procedures used in female urology. Cystoscopy is indicated when patients have symptoms or UTI after mid-urethral sling, to

Figure 1 - Rupture of vaginal vault prolapse.

Figure 2 - Cystoscopy in a patient with dysuria and interrupted flow. Notice the blue thread (needle suspension) and the stone.

rule out bladder or urethral perforation and secondary stone formation. Because there is a risk of COVID negative get nosocomial infection, the use of trans labial non-invasive ultrasound might be considered.

Regarding urodynamics, as COVID-19 may have fecal transmission and a rectal balloon is used to indirectly measure abdominal pressure for calculating detrusor pressure, urodynamic should be postponed for six months or until it is safe to be done. Most of the recent guidelines for resuming elective procedures or surgery are suggesting observing local scenario (low numbers of infected people or consecutive reduction of the number of cases for at least, 14 days) (11).

CONFLICT OF INTEREST

None declared.

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Summary and considerations in genitourinary cancer patient care during the COVID-19 Pandemic

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ABSTRACT

Purpose: To provide a summary and recommendations for the set-up of strategies for cancer patients care in genitourinary oncology clinics during the pandemic and in the recovery period.
Material and Methods: A non-systematic review of available literature on the management of urological malignancies during the COVID-19 pandemic was performed to summarize recommendations to improve the diagnosis and treatment of urological cancers during and after the contingence, including clinical and research aspects.
Results: Urological cancer diagnosis and management should be tailored according to the severity of the COVID-19 crisis in each region and the aggressiveness of each tumor. Clinicians should adhere to strict protocols in order to prioritize the attention of patients with high-risk malignancies while optimizing resources to avoid the saturation of critical care services.
Conclusions: During the COVID-19 pandemic urological cancer care has been severely impaired. For proper patient management, multidisciplinary approach is encouraged tailoring therapy according to COVID-19 regional behavior and local institutional resources. Patients with high-risk malignancies should be prioritized.

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INTRODUCTION

In recent months, the new coronavirus (SARS-CoV-2) disease (COVID-19) became an epidemiological phenomenon that has overwhelmed health care systems globally (1). The negative impact of this pandemic has involved multiple aspects of clinical practice and health services all around the World, including Genito-Urinary Oncology (GUO) clinics.

The consequences of this crisis on cancer patients care is two-fold: a) those diagnosed shortly before or during the outbreak will experience a delay on their treatment; b) new patients with potentially high-risk malignancies will undergo a delayed diagnostic process with the inherent risks due to late approach and therapy, such as progression and losing the chance of curability. In addition, cancer research has been affected, impairing many fundamental steps of clinical investigation, including patient enrolling

on clinical trials, follow-up and adverse event assessment (2).

Therefore, our objective is to provide some recommendations for the set-up of strategies for cancer patients care in GUO clinics during the pandemic as well as in the recovery period, considering that some modifications implemented to consultation areas, schedules and facilities might be in place for a while.

MATERIAL AND METHODS

On May 8th, 2020 we performed a non-systematic review of available literature through online search engines (PubMed, Web of Science and Science Direct). We looked at recommendations and the management of urological malignancies during the COVID-19 pandemic. We explored Pubmed database, American Confederation of Urology (CAU) library, European Association of Urology (EAU) recommendations, American Urological Association (AUA) COVID-19 Information Center and American Society of Clinical Oncology (ASCO) Coronavirus resources looking for publications on the aforementioned topics. After analyzing the content of selected peer-reviewed papers, we summarized some recommendations to improve the diagnosis and management of urological cancers during and after the pandemic, taking into account clinical and research issues.

GENERAL RECOMMENDATIONS

A variety of logistic considerations have to be taken into account during this pandemic when it comes to care of patients with cancer. First, clinicians working in GUO clinics should be aware whether their institutions are becoming temporary centers providing service exclusively to patients with COVID-19 or not. In this case, a strategy to timely refer patients to supporting clinics should be established in order to avoid delay in diagnostic and therapeutic procedures. Second, for those institutions treating both patients with and without COVID-19, clinicians should adhere to strict protocols in order to prioritize the attention of those with high-risk malignancies as well as to optimize resources to avoid the saturation of critical care services.

For the case of cancer care during this emergency, clinical pathways should be tailored according to the severity of the COVID-19 crisis in each region and the aggressiveness of each tumor.

On other hand, the high number of infected health care professionals in Europe suggests that clinicians should wear personal protective equipment properly at all times when performing surgical procedures (3).

Prostate cancer

Diagnosis

According to current estimates, patients at risk of being diagnosed with prostate cancer (PC) are also at risk of having worse outcomes if they get infected with SARS-CoV-2 (i.e. men older than 65 years with comorbidities). Therefore, a reasonable strategy is to delay PC diagnostic process until the critical phase of COVID-19 pandemic has passed (4), especially for those individuals with low-risk features. In contrast, for patients with high-risk characteristics, including rising serum prostate specific antigen (PSA) levels, suspicious digital rectal examination (DRE) or PI-RADS 3 or higher on multiparametric magnetic resonance imaging (mpMRI), an individualized decision-making process is guaranteed (5). If diagnosis is imperative, prostate biopsy should be performed according to each patient's SARS-CoV-2 infection status (5). In non-suspicious cases, prior testing for SARS-CoV-2 is advisable to rule out an asymptomatic infection; if negative, treating physician may proceed with biopsy process, while taking all precautions to avoid transmission during the procedure (due to false negative rates of SARS-CoV-2 testing). On the other hand, patients with suspicious or confirmed COVID-19 should wait until the resolution of infection and testing becomes negative. Regardless of patient's SARS-CoV-2 infection status (including asymptomatic patients), it is strongly advised that health care professionals use complete protection against infection when performing invasive procedures, if possible three-level protection standards (6).

Treatment

Localized and locally advanced disease

For patients with low-risk disease

(T2a, Grade group 1, PSA<10 ng/mL), active surveillance (AS) is the best option. If focal therapy is considered, it may safely be delayed until the pandemic is under control (4).

For intermediate- (T2a-T2c, Grade group 2 or 3, PSA 10-20 ng/mL) and high--risk (T3a, Grade group 4 or 5, PSA >20 ng/mL) patients suitable for radical prostatectomy, a treatment deferment of up to 6 months has not been associated with adverse outcomes (7). If External Radiation Therapy (RT) is considered, the addition of neoadjuvant Androgen Deprivation Therapy (ADT) allows for a safe delay of RT until the resolution of the pandemic while hypofractioned RT may help to reduce health care burden and patient risk of exposure (4).

Advanced disease

In case of metastatic hormone-sensitive disease (mHSPC) and first-line therapy for metastatic castration-resistant disease (mCRPC), androgen-receptor-axis targeted therapies (ARATs) in addition to ADT are the preferred option over systemic docetaxel-based chemotherapy to reduce the risk of neutropenia during the pandemic (8). If ARATs have been used previously, a patient-clinician joint decision should be taken to assess the deferment of docetaxel initiation; the individual risk of COVID-19 adverse outcomes; and inherent logistic difficulties regarding the administration of intravenous agents during the pandemic. For patients with mCRPC and bone-only metastases, Radium-223 may be a better alternative if available (8). When possible, the use of glucocorticoids should be minimized (4).

Urothelial cancer

Bladder cancer

Diagnosis

Patients with bladder cancer are also at higher risk of adverse outcomes from COVID-19 since they are frequently older than 65 years, commonly former or current smokers and have other comorbidities (i.e. hypertension, obesity). Patients with newly onset macroscopic hematuria should be evaluated with urinary cytology, imaging and office cystoscopy. For individuals with suspected or previously identified low-risk non--muscle invasive bladder cancer (NMIBC), delaying cystoscopic surveillance could be safe (4). In contrast, according to a recent surgical classification designed to improve the management of uro-oncological diseases during the pandemic (3), transurethral resection of bladder tumor (TURBT) should be considered a non-deferable procedure high-risk NMIBC, whether it is diagnostic or therapeutic.

Treatment

Non-muscle invasive bladder cancer

The evolution of low-grade NMIBC tends to be indolent in the majority of cases. Thus, during the COVID-19 pandemic, AS is an acceptable option (4).

High-grade NMIBC could be better treated with TURBT and induction Bacillus Calmette-Guérin (BCG) intravesical instillations (6 weekly) followed by one maintenance course (3 weekly). Re-staging TURBT (second look) is strongly advised in high-risk patients particularly if muscle was absent in the baseline resection (4). Radical cystectomy (RC) for high-risk NMIBC should be discouraged during the acute phase of the pandemic.

Muscle invasive bladder cancer

Delaying RC in muscle invasive bladder cancer (MIBC) for more than 90 days is associated with worse outcomes. Thus, surgical management in this scenario should be individualized. The risk-benefit balance of neoadjuvant chemotherapy should be assessed to reduce toxicity. Bladder-sparing trimodality treatment could be an option for MIBC during the COVID-19 crisis (4).

Advanced bladder cancer

Multidisciplinary approach is crucial in this situation in order to avoid treatment interruptions. If platinum-based

chemotherapy is recommended, risks and benefits should be evaluated (4). In properly selected patients with low-volume disease, the deferment of chemotherapy could be considered (8).

Upper tract urothelial carcinoma

Diagnosis

During this pandemic, the workup of patients with suspected upper tract urothelial carcinoma (UTUC) should be limited to urinary cytology and computed tomography (CT) urography (3). Diagnostic ureteroscopy should be performed only if it is mandatory.

Treatment

In case of low-risk UTUC, nephron-sparing strategies could be considered (5). For high-risk UTUC, radical nephroureterectomy could be safely delayed for up to 12 weeks in recently diagnosed patients (4). Therefore, treatment options should be discussed carefully in a multidisciplinary team.

Renal-cell carcinoma

Diagnosis

As with PC and BC, renal-cell carcinoma (RCC) patients are at higher risk of COVID-19 due to comorbidities (older age, hypertension). The initial workup, including renal mass biopsy, for patients with small renal masses (<4 cm) could be delayed until the contingency is over (4). For patients with gross hematuria or back pain, an imaging-based approach is advised.

Treatment

Localized and locally advanced RCC

AS is the preferred alternative for SRM and T1 tumors in the current emergency. For tumors suitable for nephrectomy (T1b and T2), delays of 3 to 6 months appear not to be deleterious (4). Patients with T3 tumors, especially those with inferior vena cava involvement and those at higher risk of symptomatic or oncological progression should be prioritized (3).

Metastatic RCC

During the current epidemiological situation, upfront cytoreductive nephrectomy is discouraged and should only be reserved for severely symptomatic patients due to untreatable pain or gross hematuria with clot retention (4). For asymptomatic patients with low- and intermediate-risk International Metastatic RCC Database Consortium (IMDC) disease, AS could be considered. In poor-risk patients, oral vascular endothelial growth factor (VEGF) targeted therapy is associated with lower risk of toxicity-related admissions in comparison to immunotherapy agents (4, 8).

Testicular and penile cancer

Information regarding the effect on therapy delay in these two malignancies is lacking. Given their natural history, it seems advisable not to postpone primary surgical management in localized disease. For intermediate and poor prognosis metastatic germ-cell tumors, chemotherapy should be administered without delay.

FUTURE DIRECTIONS

Among the invaluable devastating effects of this outbreak is the delay of thousands of elective surgeries and other outpatient invasive procedures all around the World in an unprecedent effort to save resources to face the contingency. Although urological practice has been impacted in different aspects (9) some learnings left by this emergency arise: 1) surgical teams are encouraged to adopt comprehensive preoperative medical optimization protocols to reduce the risk of postoperative complications while enhancing the use of hospital resources; 2) diagnostic testing that do not contribute to improve patient outcomes should be eliminated (i.e. daily chest radiographs, daily laboratory tests, urinary cultures to assess asymptomatic bacteriuria or isolated fever in a recently operated patient); 3) the establishment of formal telemedicine programs will allow for care provision while reducing the need for patient

mobilization and exposure to dangerous environments. In summary, beyond the tragic effects of this emergency, several opportunities for improvement have arisen as a result of the crisis (10).

CANCER RESEARCH DURING COVID-19 PANDEMIC

Basic and clinic research is likely to be severely affected by a pandemic. There will most likely be a decrease in trial initiations and accruals and the pace of progress will slow (11). However, the impact will be magnified, perhaps exponentially by protocol deviations and violations for missed and delayed visits, leading to countless queries and estimated dates of confinement. During the Pandemic, there is a need to carefully reconsider the clinical GUO research processes and procedures that contribute to data integrity and patient safety versus tasks that might ultimate detract from cancer research goals. On March 18 2020, the FDA published guidance for industry, investigators and institutional review boards on conduct of clinical trials of medical products during the COVID-19 Pandemic (12).

CONCLUSIONS

The COVID-19 pandemic represents one of the biggest challenges to modern health care history. Urological cancer care has been severely impaired. For proper patient management during this pandemic, multidisciplinary approach is encouraged. Treatment should be tailored according to COVID-19 regional behavior and local institutional resources. Patients with high-risk malignancies should be prioritized. This emergency represents a great opportunity to improve daily clinical practice.

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CONFLICT OF INTEREST

None declared.

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Impact of the COVID-19 pandemic on the sexual behavior of the population. The vision of the east and the west

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ABSTRACT

The COVID-19 pandemic has radically changed the way of life around the World. The state of alarm has forced the population to stay at home, radically changing both interpersonal and partner relationships; work at home, social distancing, the continued presence of children at home, fear of infection and not being able to physically meet with others have changed most people's sexual habits. We conducted a review by exploring the impact of the COVID-19 pandemic on sexual behavior in the population from three different countries: Iran, Italy and Spain from each country's perspective. The impact of the coronavirus will be very important in the sexual life of the people and we will attend in the next months or years, to some changes in the relationships at all the levels. The pandemic will negatively affect sexual behaviors due to multiple contact restrictions. In the future, we will be able to assess these effects in more detail.

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INTRODUCTION

Sexual relations suffered a serious blow due to the world pandemic from SARS-Cov-2 (1). COVID-19 has radically changed social relations in the World, both because of the restrictions imposed by the various States and because of the feeling of fear of the contagion that has swept the general population. These changes overwhelmed us in a very short period of time, without leaving time for our mind and bodies to get used to the new situation. The anguish about the world situation, together with the continuous exposure to images of disease and death, has severely tested

the emotional stability of each person. In the literature, various studies looked at the general population's psychosocial responses to the severe acute respiratory syndrome epidemic. The topics in the psychological responses included anxiety, fears, depression, anger, guilt, pain and loss, post-traumatic stress and stigma (2). The upheaval of the daily routine, the limitation of everyone's freedom and independence, and the loss of that sense of utility, proper to contributing to community work, have instilled in man a sense of helplessness and loss. From this it is clear how the psychological implications have been devastating and certainly the sexual sphere is the one that has been most affected (3). The fear of contagion itself has therefore reduced physical contact within couples, from simple kissing to full sexual intercourse. The state of constraint to which we were forced to live, side by side for 24 hours a day, the limitation of one's own space and the obligation to share every moment of the day, in some cases exacerbated the quarrels within the cohabiting couple, it exacerbated the differences of opinion, thus weakening the couple bond. Negative emotions are known to negatively affect sexual intercourse. In fact, sexual and reproductive health is a state of physical, emotional, mental, and social wellbeing in relation to all aspects of sexuality and reproduction, not merely the absence of disease, dysfunction, or infirmity. Furthermore now, with many countries in lockdown, sexual habits can also vary significantly (4). Therefore, a positive approach to sexuality and reproduction should recognise the part played by pleasurable sexual relationships, trust, and communication in the promotion of self-esteem and overall wellbeing (5). So COVID-19 has had a negative impact not only in terms of affectivity but also in terms of sexual relationship. In relations between cohabitants, sexual intercourse was affected by the continuous presence of children in the home, given the closure of schools, with the difficulty of finding a moment of intimacy. Sexuality is also influenced by the sense of desire for the other. Psychological factors, specific mood states can inhibit sexual desire. Depression and anxiety have been mostly associated with low levels of desire (6, 7). Those who live a stable relationship but are not living together, on the contrary, have a strong desire for the other, who however cannot be satisfied for the physical distance and the impossibility of approaching due to the restriction in the movements of people imposed by the State. In this case, sexuality can be experienced differently thanks to the use of the Internet, but not all couples are willing to have sex online. As for singles, it is clear how, at a time when social relationships are zeroed, it is difficult to be able to undertake occasional sexual relations, given that there is no opportunity to meet the partner. It should be noted that even the sexual relations between colleagues at work no longer have an opportunity to exist, for those workers whose companies have been closed and smart working has been adopted.

Finally, extra-marital sexual relations are made difficult by the inability to move and reach the home of others due to the legal restrictions imposed by their country of origin, but also by the fact that the respective cohabitants are at home, therefore with the inability to find a suitable place for sexual intercourse. So, if on one hand the psychological implications make the execution of the sexual act less desirable, on the other hand also logistical problems reduce the possibility of having a sexual relationship. When the state of alert is over, a lot of work will have to be done, especially on the couple, to return to normal.

SARS-CoV2-Transmission and the Sex

In terms of risk and transmission of SARS-CoV-2 during sex, some studies have showed that, the largest amount of virus is present in saliva and, so kissing, a very common practice during sexual intercourse at the pandemic times, is very risky. Furthermore, we should also consider a fecal-oral transmission has been detected in stool samples of infected patients (8, 9).

There is no evidence that the COVID-19 can be transmitted via either vaginal or anal intercourse. There is also evidence of oral-fecal transmission of the COVID-19 and that implies that anilingus may represent a risk for infection. For homosexuals spread from anal intercourses & oral- fecal way is possible. The pregnant infected women who had vaginal delivery did not have infected babies, so trans vaginal involvement did not seem.

SARS-CoV-2 can be present in the semen

of patients with COVID-19, and SARS-CoV-2 may still be detected in the semen of recovering patients. Owing to the imperfect blood-testes/deferens/epididymis barriers, SARS-CoV-2 might be seeded to the male reproductive tract, especially in the presence of systemic local inflammation. Even if the virus cannot replicate in the male reproductive system, it may persist, possibly resulting from the privileged immunity of testes. If it could be proved that SARS-CoV-2 can be transmitted sexually in future studies, sexual transmission might be a critical part of the prevention of transmission, especially considering the fact that SARS-CoV-2 was detected in the semen of recovering patients. Abstinence or condom use might be considered as preventive means for these patients (10).

Sexual Health during the Pandemic

Physical Benefits: There are indications that sexual activity is an integral contributor to quality of life and overall physical health. It has long been understood that poor health can affect sexuality. Diabetes, chronic pain, depression, heart disease and cancer are all examples of conditions that can impair most areas of sexual function.

In pandemic times, management interventions including prolonged periods of quarantine, social distancing, and home confinement, have all-pervasive effects on social and economic life. Regrettably, little information and attention is focused on maintaining sexual health, despite its powerful effect on the overall quality of life in the short and long-term.

Psychological Benefits: WHO defines mental health as "a state of complete physical, mental and social well-being" and not merely "the absence of disease or infirmity." Regarding pandemic periods, mental health is an extremely essential issue that should be noted (11, 12). According to the literature, the most prevalent symptoms in those who have been quarantined are depressed mood, irritability, fear, nervousness, and guilt (13, 14). Scientific evidence has shown a strong link between mental and physical health. Daily activities such as sexual practices are highly related to a person's quality of life and mental health. The negative psychological effects like depressed mood, irritability, fear, nervousness, and guilt during this period are not surprising (2, 16). Other studies have also demonstrated a positive association between duration of quarantine and worse mental health, more specifically symptoms of post-traumatic stress, (PTS) avoidance behaviors and anger (15).

Another key condition is the frustration/boredom of confinement, loss of routine, and social and physical contacts, which seems to be exacerbated when it is not possible to carry out daily activities or to participate in social networking activities.

The long-term effects also appear to be problematic. According to a study carried out with a group of individuals who were quarantined for potential contact with SARS-CoV-2 in the weeks after the quarantine period, a significant percentage of individuals continued to avoid others who were coughing or sneezing, closed places with clusters of people and public spaces. On that note, it is essential to reduce boredom, enhance communication and to activate social contacts, since the impossibility of doing so is a cause not only of immediate anxiety, but also of long-term distress (16).

Sexual health is essential for global health and well-being of individuals, couples and families. Studies correlate sex with increased satisfaction with one's mental health, increased levels of trust, intimacy, and love in relationships, improved ability to perceive, identify, and express emotions and lessened use of immature psychological defense mechanisms (17).

To conclude, the psychosocial and economic implications of the current pandemic and the impact they have on collective, dyadic, and individual adjustment, are expected to have deleterious collateral effects on general health.

Sexual desire and desire discrepancies: Concerns around low sexual desire are highly prevalent across populations, ranging from 10-40% and are one of the most widespread sexual problems adults face (18). However, sexual desire discrepancy (when partners report significantly different desires for sexual intimacy) remains one of the most common reasons for couples to seek therapy services due to the negative impact on relationship and sexual satisfaction.

Erectile Dysfunction

Erectile Dysfunction (ED) is the most common male sexual health concern, affecting between 13-28% of men aged 40-80 years (19), with prevalence increasing with age. While there is no data that explores the relationship between COVID-19 and the additional risk of developing ED, men at greatest risk for having serious complications secondary to COVID-19 are also those traditionally at risk for ED: older adult, diabetic, men with cardiovascular disease, overweight/obese, and with multiple comorbidities (20). Therefore, it is important to consider the role of added stress, anxiety, and physical health implications for men with ED amid the COVID-19 pandemic.

It is not clear, if that COVID-19 may add to the collective risk of developing ED or exacerbate existing ED in men who contract COVID-19; there are previous examples of viral respiratory infections complicated with fibrosis (21). Chronic lung diseases, namely interstitial lung diseases and chronic obstructive pulmonary diseases (COPD) have been associated with ED. In conclusion, despite lack of research on the topic, we may expect ED to worsen during the highly stressful situation men face during the current pandemic. Postponement of most elective, non-urgent medical treatments and putting "on hold" topics that are not a direct, immediate threat to one's health and safety may have a negative impact also on men's sexual health.

These days quarantine time affect on mood of all people and decrease libido and sex because of bored at home, but in another side, since people are staying home without job, they need to have sex with their partner. Since sex relationship affects to immune system, and boost immunity against virus infection, avoiding sex is not recommended.

Dating and Sexual Activity during the Pandemic

Physical distance is necessary to control the pandemic, so physical dating have disappeared. It is natural that increased levels of stress can reduce this urge, but social distancing and stressful circumstances also increase the need for emotional bonding. We restructured and concluded here important issues to remember during pandemic for maintaining safe and pleasant sexual activity:

Sex life during the pandemic

Undoubtedly, a new era is present, and we must prepare for the different pandemic and post-pandemic scenarios. The truth is that we still have more questions than answers, and we are currently in the middle of COVID-19 pandemic, a true fact: There isn't any scientific data yet on how this might impact people's sexual and relational lives.

But we can go back to the historical data to help us raise those possible scenarios. Perhaps it can be a window to recreate campaigns during the years of HIV epidemic, making safe sex sexy or could be an open window to create an "immune passport" for coronavirus and let us take advantage to de-stigmatize STD (Sexual Transmitted Diseases) screenings and including them in this type of documents to establish safer sex and not only sex free from coronavirus. So, the main effect is that currently, our society, need to incorporate new COVID-19 sex status.

But, it seems that current debate in the community which deals with sexual health is related to whether there will be an increase in sexual activity and therefore create a new baby boom, or the opposite, the acute anxiety that a crisis supposes and the uncertainty in front of a real and global threat against life, added to the grief for many losses, may would be an erotic killer, and produce more depression and less sex. But even in a society under survival mode, sexuality has a space, because it is a fundamental expression of the human experience. In the broad picture, many people are in lockdown with limited outside activities, staying at home is an opportunity for physical intimacy, assuming you have a live-in sexual partner, of course and be more creative in developing tools for intimacy it´s always an option. The main issue here, it is about how to maintain a safe intimacy during and after pandemic times, keeping the adventure and pleasurable feelings at same time alive.

For sure, a new rule has arrived and many forms of intimacy require a closer distance than the six feet of separation recommended by the Centers for Disease Control and Prevention (CDC) (22). But our current digital culture is well-positioned to facilitate shifting models of sexual interaction. Allowing society to have the chance to choose being

more resourceful which means a great time to be mindful of our sexual health, which has proven benefits beyond pleasure. But we know that women and men sexual response have different drivers and different response model, one more circular, female and the other more lineal. But the immediate effects in people sex life, independently of their status or gender would be to try to keep safety over pleasure aside, from figure out how to maintain social connection without breaking the guidelines.

And how to reorder pleasure, intimacy and sexual activities with a partner when mandates requires avoiding sex contact and when your safest sex partner, after yourself, is someone you live with according to NYC health department (23). It seems pretty challenging. Even more in our western society, where sexuality has being framed more into an efficiency and accomplishment model than pleasurable, creative and imaginative one. We live in a society where there is a common belief, a cultural and interpersonal expectation that sex should always be "amazing" and with a "perfect" performance. When this is not the case, we consider it inappropriate and understand it as a symptom of "lack of love or affection" or even as a defect in the relationship (24). So, enhance no physical interaction could lead to a new way of sexual behaviour, motivators and triggers for well function or dysfunction, as well. Maybe this new normality could shift models of sexual interaction and we will have the need to research on this new intimacy and sexual behavior for both genders and regardless of their relationship status.

By the moments, people need to be aware, that some may have the virus and not yet have symptoms during the early incubation phase (22) and it could be an issue for who are single and in the active search for a partner, during pandemic avoiding physical contact is what corresponds and then it will be necessary to take measures according to the new findings. Additionally, some people never develop obvious symptoms. For this group, masturbation, sexting phone sex with a partner who doesn't live with them, and intimate devices (used just by the holder person) could enhance self-eroticism and lead men and women to new ways of self-exploration if the interest and sexual desire allows to those activities.

And for those who have sexual partners and have not being exposed to COVID-19 and are healthy, practicing social distancing and have had no known exposure to anyone with COVID-19, sex contact, kissing and touching are more likely to be safe as sharing same space or bed should not be an issue.

The role of fears and anxiety and obsessiveness on sexual dysfunction in quarantine time

The need to feel safe and adventurous at same time during quarantine can be complicated, in fact it is one of the challenges for long-term relationships couples to maintain healthy interest and sexual desire alive in regular "non-quarantine" conditions. We are submerged into an anti-erotic culture resulting from the obsession and optimization for efficiency and perfectionism of sexual performance and this explains much of the low fulfillment of expectations around sexuality (26). In addition, we must take into account, not only the fear and uncertainty existing around how to keep a pleasant and safe sexual activity in quarantine, but also the uncertainty about definitive data regarding fertility, vertical transmission and sexual transmission of COVID-19.

Fear, guilt and anxiety are part of the limiting emotions for a fluid and pleasant sexual response and explain the appearance of some of male and female psychogenic sexual dysfunctions. Especially the well-known performance anxiety.

And what we expect is to find a variability in sexual manifestations in front of chaos and that they would be even dynamic and changing according to how the situation transitions, from the pandemic acute phase to reordering our life by living with COVID-19. So, for those men and women with higher levels of sexual inhibition and lower levels of sexual excitation will find them more vulnerable to sexual response alteration during this time (26, 27).

Maybe it is too soon to forecast an increment for sexual dysfunction or an improvement of sexual function due to fear or anxiety, because human sexuality is thus a complex phenomenon with many contributing factors, from the psychological to social to the biological and there are as many sexualities as there are humans.

Sexual activity during the COVID crisis- an ongoing survey

Due to the limited information currently available regarding sexual activity during the COVID-19 pandemic, Garcia Cruz and Peraza have create a survey in English and in Spanish version with the objective to explore the sexual behavior during the COVID-19 Pandemic in terms of sexual intercourse, masturbation and sexting; it was conducted from March to April 2020. and distributed via social media (Twitter, LinkedIn and Facebook). A total of 279 (100%) answers were obtained with 58% women, 40% men, 1 transsexual man, 1 transsexual woman and 3 people who labelled themselves as "other".

Sexual intercourse

García-Cruz and Peraza´s preliminary results showed out that sexual intercourse has not been affected (less frequent in 31%, same frequent in 41% and more frequent in 14%, no couple 15% in English speaking population report; when was compared the Spanish speaking population: less frequent in 23%, same frequent in 39% and more frequent in 7%, no couple 30%). Surprisingly, a total of 3.2% vs 9.7% in the Spanish and the English population respectively had sexual relationship with different people from their partner during the quarantine.

Masturbation

García-Cruz and Peraza survey also addressed this topic, finding that only 10% of the surveyed people considered themselves to be practicing more masturbation during the lockdown. In this specific matter, our survey pointed that 16% of the survey was using chats and social media for sexting and another 5,5% dating apps.

The amount of spare time, the theoretical lack of intimacy with other people and the stress generated by the situation might have led to a rise in masturbation. Besides, as commented above, a significant rise in porn consumption has taken place. The lack of intimacy and the general concern about the global situation can be offered as an explanation for this finding.

Sexting

The results of the survey showed that sexual communication via digital strategies would be a good alternative to maintain a certain level of sexual activity.

Although we have been advised to limit social interaction, it is hard to believe that sexually active couple have fully full fit the request of absolute limitation of intimacy. On the other hand, the closure of educational system has led to a lack of intimacy that, together with the general concern and negative thoughts about the present and future situation, might lead to a diminish of sexual drive and activity.

INCREASE IN PORNOGRAPHY

One of the few sectors that has been benefited from the coronavirus pandemic has been the pornography websites that have experienced meteoric growth. The state of alarm has forced the population to stay at home, radically changing both interpersonal and partner relationships; work at home, social distancing, the continued presence of children at home, fear of infection and not being able to physically meet with others have changed most people's sexual habits.

The consumption of pornography reflects this new situation as reflected in the statistics of Pornhub (28), one of the leading pornography portals worldwide, which has published data on this substantial increase in visits to its website. During this period, this website offered free access to its premium version to everyone to encourage the importance of staying at home and practicing social distancing. Pornhub was founded in 2007 and has more than 120 million visitors per day with an average of 100 billion video views per year. The website receives 36 billion visits per year.

Worldwide traffic to Pornhub

Worldwide traffic to Pornhub skyrocketed compared to the situation before the pandemic in February 2020 with an elevation that reached its peak increase of 24.4% happened on March 25th after it offered its free premium site to encourage people to stay indoors and distance themselves socially.

Weekly Traffic Changes

Italy was the first European country to clo-

se its borders and put into effect a nation-wide quarantine. The following chart shows how Italy's traffic changed over the last few weeks. The drastic increase of 57% in March 12th, 2020, came after Pornhub offered free Premium service to all of Italy. The same offer of free Pornhub Premium was made beginning in March 16th to the countries of Spain and France. Traffic from Spain increased 61.3% (28).

Hourly Traffic Changes

Traffic on March 17th was up all over the World, but we can easily see what times the most significant changes had happened when compared to an average day. The largest increase of 31.5% happened in the early morning around 3am. We can surmise that people stayed up later because they didn't need to go to work in the morning and slept in a little longer. Traffic at 1pm was 26.4% higher than normal when people may otherwise be at work (Table-1).

As most of the country was required to stay inside, major changes were observed in Italy's hourly traffic. On March 11th, traffic at 2am was 47% higher than normal and remained 25% above average even at 5am. Evening traffic at 9pm was 12% higher than 9pm on an average day.

Traffic from Spain was 6.1% higher than normal on March 12th. After midnight, traffic increased up to 10.1% at 3am. Early morning traffic was much lower than average, followed by a slight increase in the afternoon and a 6.5% increase at 7pm (27).

DIVORCES

How the pandemic situation may affect relationships will have to be studied in the future. The pandemic is radically changing couple and sexual relationships: confinement, difficulty in having sex, loss of work, economic problems and an uncertain future can act as triggers to break up many couples. Many weddings have been postponed, and if previous relationship problems already existed, the confinement situation may accelerate this process. In China, where the coronavirus has forced millions of people into isolation, the number of divorce applications has soared in recent months in the provinces most affected, according to local newspapers in these provinces. In Hong Kong's general population in 2004, divorce applications were 21% higher than 2002 levels. The psychological and economic impact of this pandemic will last for months after the return to normal.

CONCLUSIONS

The truth is that we still have more questions than answers. In the upcoming months and years, we will be able to assess these effects in more detail, but we are sure that COVID-19 will have a negative impact not only in terms of affectivity but also in terms of sexual relationships. The impact of the coronavirus will be very important in the sexual life of the people and we will attend in the next months or years, to some changes in the relationships at all the levels.

Table 1 - Worldwide Traffic to Pornhub.

World Hour Traffic Changes	Traffic Increase	Hour
March 17th	31,5%	3 am
	26,4%	1 pm
Italy Hour Traffic Changes		
March 11th	47%	2 am
	25%	5 am
	12%	9pm
Spain Hour Traffic Changes		
March 12th	10,1%	3 am
	6,5%	7 pm

Psychological, social and the biological factors should be investigated regarding an increment of sexual dysfunction due to fear or anxiety, since human sexuality is a complex phenomenon with many contributing factors.

General recommendations that can be made are that starting a new relationship is so risky because maybe one of them is infected and having non-monogamous sex also is risky. The only safe way is having sex with primary or monogamous sex, if one of them do not go outside or have a risky job.

On the other hand, the consumption of pornography reflects this new situation with data that show a substantial increase in visits to those websites. The pandemic is radically changing couple and their relationships: confinement, difficulty in having sex, loss of work, economic problems and an uncertain future can act as triggers to break up many marriages. The psychological and economic impact of this pandemic will last for months after the return to normal.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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COVID-19: Measures to prevent hospital contagion. What do urologists need to know?

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ABSTRACT

A new outbreak of respiratory infection caused by the novel coronavirus in late December 2019 in China caused standards of medical care to change not only for related areas but for the entire healthcare system, and when the WHO declared COVID-19 a pandemic new strategies of patient care had to be defined initially to optimize resources to confront the pandemic and then to protect healthcare personnel. As urologists, we must be involved in these new standards, since without an effective vaccine the risk of contagion is high; thus, the purpose of this review is to have orientation on the measures urologists should take in their everyday clinical practice.

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INTRODUCTION

On December 31, 2019, 27 cases of pneumonia of unknown etiology were identified in the city of Wuhan, Hubei Province, in China. The characteristic manifestations seen in these patients included clinical symptoms of dry cough, dyspnea, fever, and bilateral pulmonary infiltrates in the images. All these cases were related with the Huanan wholesale seafood market in Wuhan, which sells fish and a wide variety of species of live animals, including poultry, bats, marmots, and snakes [1]. On January 7, 2020, the causal agent was isolated from nasopharyngeal swabs and was named SARS-CoV-2 by the World Health Organization (WHO), which causes the disease COVID-19. Although a majority of cases have resolved spontaneously, some have developed various fatal complications which include organ failure, septic shock, pulmonary edema, severe pneumonia, and acute respiratory distress syndrome (ARDS), which require management in an Intensive Care Unit (ICU) [1].

Clinical characteristics of COVID-19

The SARS-CoV-2 virus is transmitted predominantly through aerosolization, particles from respiratory droplets or secretions; human-human transmission has been confirmed. As with any viral disease, maintaining a proper distance of at least 2 meters is one of the basic measures for prevention [2]. It is clear that the elderly and patients with chronic cardiopulmonary diseases are especially vulnerable, although numerous deaths have also been reported among patients age 50 years or less without comorbid conditions [3]. Various characteristics of the disease have been described as it advances through different stages. The disease COVID-19 is mediated by the virus bonding to "peak proteins" to coreceptors of the human Angiotensin-Converting Enzyme (ECA) concentrated in the lungs; however, they are also expressed in the brain, heart, kidneys, and gastrointestinal tract [4, 5].

Optimizing resources

As hospitals start preparing for the possibility of high demand for care for cases of COVID-19, optimizing resources by cancelling elective surgeries will increase access to care [6]. Hard decisions have to be made on which surgeries should continue under present circumstances and elective procedures postponed until the pressure on the hospital system to provide care for patients with COVID-19 cases [6].

The choice of urgent or emergency surgery will depend on capacity and demand without overlooking diagnosis, and at the same time should be counteracted by the effects of delaying surgery and in particular genitourinary neoplasms and complicated lithiasic disease. Urologists can help by reducing demand for ventilators, personal protection equipment, and other critical hospital and human resources, minimizing surgeries without compromising patient outcomes whenever possible. The surgeries which should be prioritized to meet demand for care for COVID-19 and move forward are cases where evidence suggests that even short-term delays may affect the patient's survival. Also, alternatives are suggested for management of common urgent or emergency urological procedures which may prevent the use of ventilators, and we consider the use and impact of common urological treatments in patients during an infectious outbreak. Finally, although we do not incorporate the patient's age and fragility in these recommendations, the risk of postoperative COVID-19 infection and its potential impact on a patient's postoperative evolution should also be considered [7].

Shared decision making should be encouraged. To the extent possible, patients' holistic needs, like managing anxiety, should be considered when discussing decisions on postponements in treatment. To the extent possible, patients should be informed that decisions regarding elective cancer surgery are based on a consensus, are based on emerging data, and are based both on wanting to give them the best opportunities to achieve good outcomes in their cancer and minimize their risk of harm from COVID-19 [8].

General aspects

Even if there is insufficient scientific evidence on managing care for patients with suspected or confirmed COVID-19 infection who require urological surgery, there are general aspects which make up good clinical practice in prevention of events which help minimize the risk of contagion in the different stages of the procedure [9].

The high level of diffusion of the pathogen and its virulence, which has pushed healthcare systems in different countries to the point of saturation, makes it essential to know and take the relevant steps correctly to prevent contagion to healthcare providers and prevent them from becoming potential transmitters of the disease, as is seen statistically in around 10-15% of cases.

The concerns and anxiety of healthcare professionals are constantly in these cases, which should be heard, protected, prepared, supported, and cared for [10]. This makes it necessary to oblige everyone circulating in a medical care institution to use a properly fitted facemask.

Improving protection for the healthcare team

A healthy and effective HCP team is crucial to successfully prevent the ongoing epidemic from expanding further. The large number of infections underscores the need and urgency of protecting the COVID-19 healthcare team. It is praiseworthy

that during the pandemic the Chinese government has placed high importance on protecting the health of healthcare personnel and has taken a series of immediate measures [11], like better orientation on proper use of personal protection equipment (PPE), better logistics and medical supplies, and better disinfection in hotels where healthcare personnel are housed. Also, there is now an emergency tracking system to monitor all healthcare personnel exposed, which contributes to rapid detection, effective classification and isolation of infected patients. A special group of medical experts are doing everything possible to diagnose and treat medical personnel with suspected and confirmed infection. Also, a special health and life insurance fund was created for all healthcare professionals working on the front line at the national and provincial levels [12]. All these factors help guarantee the confidence and efficiency of healthcare professionals, but there is still much to do to protect their long-term occupational health even more.

Options for elective surgery

Preadmission and hospitalization of urology patients programmed for elective surgery during the COVID-19 pandemic should consider two important practical aspects, such as the need to reduce the home-to-hospital traffic flow and limited (null) access to all diagnostic tests related to preadmission. Also, it should be important to guarantee that patients coming from home do not constitute a source of contagion for hospitalized patients. Preoperative tests should be performed in a single hospital visit whenever possible, after telephone classification of COVID-19 symptoms and using preferential and well-defined hospital routes. Routine blood and instrumental tests to define the risk of anesthesiology should be performed in all patients programmed for elective surgery [13].

Specifically analyzing the ideal pathway, which is desirable in COVID-19-free hospitals in the pre-admission phase, it would be advisable to take nasopharyngeal swabs in all patients to rule out the presence of coronavirus 2 in severe acute respiratory syndrome (SARS) -CoV-2) as outpatients [14].

Based on the indications of the Centers for Disease Control and Prevention [14], it is advisable to guarantee a unique access point to facilitate detection procedures.

Excluding the risk of suspicious symptoms and signs (body temperature) of COVID-19, hospitalized patients should be asked to use a surgical mask and to observe the rules of hygiene recommended for the general population. A valid aid is to reduce the number of beds per room and/or guarantee the minimum safe distance between patients.

The recommendation to use individual protection systems is mandatory both for patients and for healthcare workers.

Bearing in mind that the majority of non-deferrable surgical procedures are performed to treat malignant genitourinary tumors [15], staging is of vital importance. In this context, although the recommendations of international guidelines should be respected, tests which are not essential for surgical planning and staging should be postponed.

Approach in the emergency ward

At Hospital Central Militar in Mexico, from the onset of the pandemic, the facility was set up to receive patients with COVID-19 without failing to attend emergencies involving other disorders, including urological emergencies; to achieve that, care was set up as follows (Figure-1).

If surgical procedures are inevitable, it is recommended that all procedures be performed by experienced urologists.

Consequently, we describe the most up-to-date information, data, and recommendations on protection of personnel in the operating theater, and how to minimize the risk of subsequent contagion, as follows:

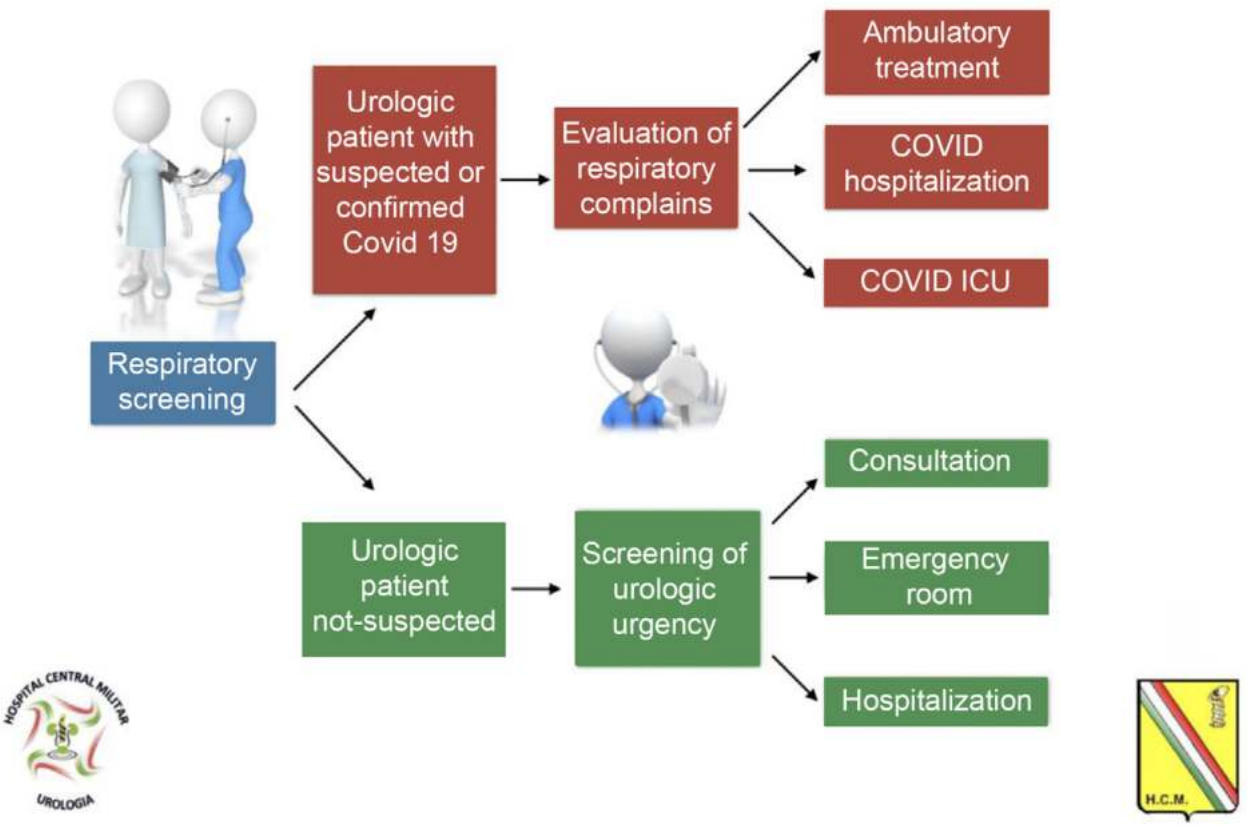
1. Preparation before surgery [16, 17]

A - Preparation of patients with suspected and/or confirmed COVID-19

☐ Validly informed consent, which includes the risk of exposure to COVID and potential consequences.

☐ Surgically treat only high-priority and emergency cases during the COVID pandemic.

Figure 1 - Approach to patients with suspected urologic emergency or with confirmed diagnosis of COVID-19 at the department of Urgency of the Hospital Central Militar.



☐ Consider elderly patients with comorbidity with severe risk of COVID infection and a fatal outcome.

B - Preparation of the operating theater [16, 17]

☐ Allow **minimum personnel** in the ward, even during the intubation procedure.

☐ Use a **smoke extractor** when using electrocauterization.

☐ Consider **avoiding laparoscopy**.

C - Preparation of the surgical team

☐ **Personal protection equipment** for each procedure performed on a COVID-19 positive patient or with suspicion of COVID-19.

☐ Respirators/N95 masks.

☐ Disposable masks or respirators.

☐ Additional **resources** on PPE.

☐ The **fit test** is essential to ensure that masks fit properly and minimize exposure.

☐ **Contagion** with the COVID-19 virus **by aerosolization and Pilger droplets** are significant risks for surgical personnel.

☐ Surgeons and personnel not necessary for intubation **should remain outside the operating theater until the process of anesthesia and intubation is completed** for patients with conformed or suspicion of COVID-19.

☐ Bear in mind how long COVID-19 may remain infectious on **different surfaces** (for example, cardboard 1 day, plastic 3-4 days).

2. Intraoperative management [16, 17]

A - Anesthetic management

☐ The type of anesthesia should be chosen based on the patient's conditions.
☐ The risk of contagion by aerosolization is increased with procedures like endotracheal intubation and tracheostomy and during pneumoperitoneum evacuation and aspiration of bodily fluids during laparoscopic surgery.
☐ Negative pressure should be maintained in operating theaters.
☐ Avoid changes of operating theater personnel (Figures 2A and B).

B - Aspects of laparoscopic and robot-assisted surgery
☐ Laparoscopic surgery may be associated with a greater quantity of smoke particles.
☐ Surgical smoke is released at low pressure in several stages of surgery.
☐ Do not insert 8 mm instruments in a 12 mm da Vinci trocar without a reduction.
☐ Do not insert a 5 mm instrument in a 12 mm da Vinci trocar even with the reduction in place.
☐ The lowest intraabdominal pressure permitted is recommended with the use of integrated intelligent insufflation systems.

C - Aspects of endoscopic surgery
☐ All procedures should be considered high risk.
☐ There is a link between urine leakage and virus transmission. However, although evidence of transmission of the disease via urine has not yet been confirmed, urine sampling (for urine culture, bars, and other analyses), urethral catheterization, and endoscopic procedures should be performed with caution.
☐ Irrigating fluid evacuated during endourological procedures should be collected through a closed system.
☐ Surfaces must be cleaned rapidly using suitable absorbents and decontaminated with chlorine (5000-10000 mg / L) or another suitable disinfectant (Figure-3).

3. Postoperative management [16, 17]

A - If it proves necessary to move a patient positive for COVID-19 or with suspected infection to a recovery area or ICU after surgery, the **minimum possible number of personnel should participate in the move.**

B - Personnel should use PPE and **should not use the** same **equipment used in the surgery**

C - Close the laminar flow and air supply in the operating theater

Figure 2 A and B - Intraoperative Management Hospital Central Militar, México.

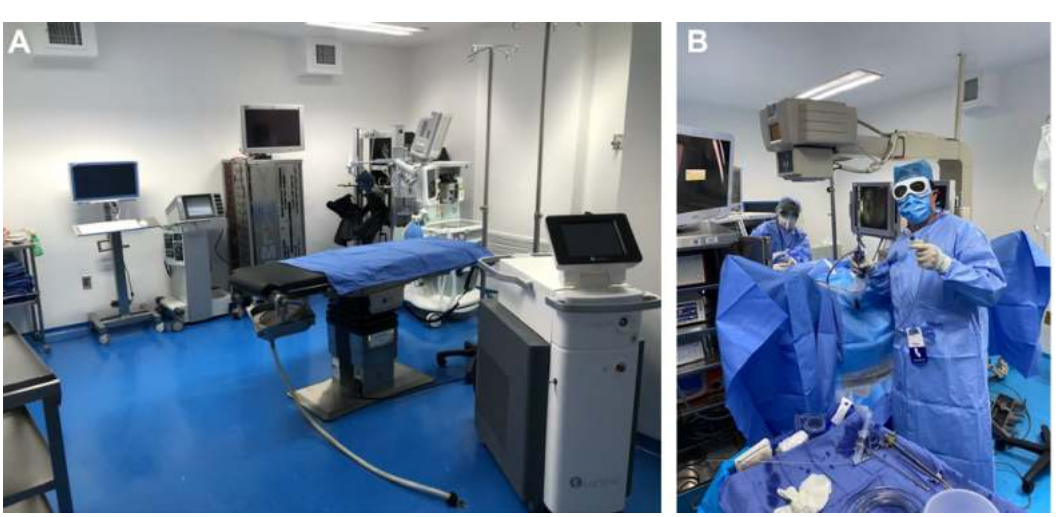


Figure 3 - Aspects of Endoscopic Surgery.

D - Sanitize the operating theater with peroxyacetic acid and reuse after 2 hours.

Looking forward

Standard guidelines and procedures should be established to detect infectious diseases at an early stage, to opportunely announce pathogens, pathways of transmission, diagnosis, and treatment among healthcare professionals. Also, improvement in professional practice as an essential part of continuing medical education in all medical and public healthcare institutions is another critical step to reduce the rate of infection among healthcare personnel. Doctors, regardless of their areas of practice, should conduct routine emergency drills for infectious diseases, receive periodic professional training in protection against occupational risks. Especially, medical personnel involved in management of infectious diseases must be well trained in proper use of PPE, and the certificate of continuing education may be mandatory for key healthcare personnel or personnel in all medical institutions. Also, ease of access to mental health services for HP should be assured throughout their professional career, especially during the crisis when they need relief from anxiety and stress.

With stabilization of epidemics and measures taken by decision makers, the scarcity of PPE in China was attenuated significantly in mid-February [18]. However, the COVID-19 outbreak alerts us that a carefully planned stockpile of PPE and other essential supplies is key in effective preparation for infectious diseases and for the healthcare team to function optimally [19]. Because an epidemic may affect a broad population, availability and proper use of PPE, such as N95 respirators, facemasks, surgical gowns, and gloves, are crucial to protect the health of HP [20]. While it is very hard to predict a widespread epidemic outbreak, all healthcare centers should stockpile a certain amount of critical PPE to guarantee an adequate supply from the outset. Furthermore, it is also important to establish a centralized and coordinated supply network for emergency PPE between central and local governments, medical care facilities, and medical teams, to meet demand for consumable and durable supplies in a prolonged generalized epidemic.

CONCLUSIONS

As urologists, we need to adapt our clinical practice to the new outlook facing us under the COVID-19 pandemic, anticipate that, as social distancing measures are lifted and until a vaccine is available, the risk of contagion will remain high for the majority of healthcare personnel, and therefore we must conduct our routine clinical and surgical urological activities without losing sight of that risk and taking appropriate and validated measures to minimize the risk of contagion among medical personnel.

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Social media influence in the COVID-19 Pandemic

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ABSTRACT

Never before in human history has it been possible to communicate so quickly during a pandemic, social media platforms have been a key piece for the dissemination of information; however, there are multiple advantages and disadvantages that must be considered. Responsible use of these tools can help quickly disseminate important new information, relevant new scientific findings, share diagnostic, treatment, and follow-up protocols, as well as compare different approaches globally, removing geographic boundaries for the first time in history.

In order to use these tools in a responsible and useful way, it is recommended to follow some basic guidelines when sharing information on social networks in the COVID-19 era. In this paper, we summarize the most relevant information on the influence, and advantages, and disadvantages of the use of social networks during the COVID-19 pandemic.

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INTRODUCTION

Social media platforms are amongst the most widely used sources of information in the World, the easy and inexpensive access to the internet and a large number of registered users in these platforms make them one of the easiest and most effective ways to disseminate information. During major events, the overall response is usually a greater search for information be it a sports event, a disease, or a natural disaster.

A good example can be seen with the peak of searches for information on the Internet and social media platforms in China preceding the peak of incidence in COVID-19 cases by 10-14 days, with which Internet and social media networks searches have a demonstrated correlation with the incidence of disease (1, 2).

Social media platforms have also become helpful for the lay public to maintain communication with friends and family to reduce isolation and boredom which have been associated with an-

xiety and long-term distress, therefore becoming an important recommendation for isolation at home to help to reduce the psychological impact (3).

Some of the most relevant characteristics of social media platforms in this pandemic has been the rapid dissemination of protocols at regional, national, and international levels. Sharing protocols about treatment, personal protection equipment, or even proposals for fair allocation in scarce medical resource settings have now become the new normal (4).

This allows centers with less capacity to develop protocols at sufficient speed to be able to implement or adapt other's protocols to their particular situation or resources in minimal time, something unthinkable 20 years ago when most social media platforms had not yet been born (5). We provided in this manuscript, the most important advantages and disadvantages associated with the use of social media platforms during the pandemic.

Advantages of social media use

Social media have the great advantage of rapid dissemination of educational content in the COVID-19 era, for example, Chan et al. (6) developed an infographic about airway management of patients with suspected or confirmed COVID-19. It was shared through Twitter and WeChat, in a few days requests were received for its translation into more than ten languages, besides the distribution allowed adapting the infographic to the particularities of each healthcare setting.

Faster dissemination of information regarding preventive measures has a lot of potentials. A recent study by Basch et al. (7) evaluated the 100 most viewed videos on YouTube with the word "coronavirus", these together had more than 165 million views as of March 5, 2020, 85% of them belonging to news channels; It was found that less than ⅓ of the videos mentioned the recommended prevention measures, less than half mentioned the most frequent symptoms, however, almost 90% commented on deaths, anxiety, and the quarantine status. This study leaves us with an important reflection on the missed opportunities for dissemination of quality information on the prevention of contagion and frequent symptoms of COVID-19 on platforms such as YouTube, which are being increasingly consulted as an information source.

When it comes to publications, studies have shown that the dissemination of scientific literature on social media platforms (Facebook, Twitter, etc.) increases the number of downloads, queries, and citations of these articles (8-10) which, with the COVID-19 pandemic are characteristics that have undoubtedly allowed rapid dissemination of knowledge worldwide, in addition to markedly reduced editorial times, which have gone from months of processing to days or weeks since its reception.

For this reason, before sharing medical information, we advise following some guidelines of responsible use of social media when disseminating information; these guidelines are summarized in Table-1.

Another advantage of social media platforms during the COVID-19 pandemic has been the possibility of arranging collaborative research projects, surveys, and multi-center studies. Finally, another advantage of social media platforms is supporting continued medical education through online live and recorded webinars through platforms like YouTube, Skype, or Zoom.

Disadvantages of social media use

Among the disadvantages, we have the possibility that information transmitted is not current, has not been subjected to peer review, is invalid, incorrect, not applicable to our environment, or even false.

Another big obstacle for social media and the dissemination of information are the "*bubble filters*", a concept coined by Eli Pariser in 2011 (11), which tells us about a "personalized ecosystem" towards the user, in which the algorithms through the data collected from the same user, predict their preferences and yield results that are considered similar to the likes of that user. These bubbles produce a loop of similar content that prevents the user from seeing other different sources to contrast information (12). This concept applies to any scenario or illness that is consulted in internet search engines or on social media platforms such as Facebook and Twitter.

Table 1 - Criteria for the responsible use of the information disseminated on social media. Modified from Chan et al. (6).

Guidelines for responsible use of social media for disseminating information
1 - Prefer dissemination through established professional platforms, or communication groups.
2 - Provide source when sharing information. Abstain from sharing information without a clear and trusted source.
3 - Abstain from sharing information that may only induce panic or anxiety.
4 - Quality should be preferred over quantity when sharing information, *In vitro* studies and low-quality evidence are of little or no use in daily practice and may give unfounded hope.
5 - Declare conflicts of interest, when appropriate.
6 - Avoid providing medical advice in social media and abstain from giving recommendations not backed by evidence as this may confuse lay public.
7 - Use transparent methods for peer review and feedback, like platforms for post-publication peer review processes or pre-print (unpublished manuscripts) like medRxiv.org, providing author/institutional contact, and pursue a traditional peer review process as soon as feasible.

Finally, probably the worst face of social media is the potential to disseminate erroneous, alarmist, and exaggerated information that can cause fear, stress, depression, and anxiety in people with or without underlying psychiatric illnesses.

A study by Wang et al. (13) in China, conducting an online survey with 1,210 responses, found that 53.8% of respondents considered the epidemic's psychological impact as moderate or severe; even a research group created and validated a scale called "Fear of COVID-19 scale" (14) to assess the level of stress and anxiety in the population and to establish appropriate measures to prevent sequels associated, such as post-traumatic stress disorder (PTSD) which was the most prevalent psychiatric sequelae after the Severe Acute Respiratory Syndrome (SARS) epidemic in Asia in 2003, followed by depressive disorders (15). Other more severe diseases or events such as suicides have already been reported in some parts of the World like India, Britain, Germany, and Italy (16).

Infodemic and disinformation

By April 30, 2020, there were more than 8,000 papers in PubMed with the word "COVID-19" (17), which tells us about the tsunami of information in less than 4 months since its appearance in China; with all the attention poured into the media, the avalanche of data becomes unaffordable, something also called "Infodemia" (18, 19).

On the other hand, at the same speed information travels, disinformation does, it is for this same reason that some authors have suggested creating working groups aimed at fighting myths and disinformation in social media platforms (20). In this way, World Health Organization (WHO) developed an exclusive section on its website designed for coronavirus myth-busting (21).

Connected with this same issue, the lay public gains access to preliminary and *in vitro* study results through newscasts practically at the same time that this information is available to the medical community, which combined with the generalized fear of the virus and healthcare systems overwhelmed, generates pressure on patients to demand such experimental treatments for themselves or their families, and doctors may feel compelled to try them, even when there is no high-quality evidence to support their use for these purposes.

CONCLUSIONS

Social media has advantages and disadvantages, the responsible use of these tools

can help during a pandemic to quickly spread new important information, sharing diagnostic, treatment and follow-up protocols, comparing different approaches from other parts of the World to adapt them to our setting and available resources, with the downside of possible dissemination of fake data, myths, and pessimist information that combined with quarantine states may lead to anxiety, depression and in some extreme cases, the suicide. Therefore, it is advisable not to contribute to the infodemic and follow a responsible use of social media when disseminating information.

ABBREVIATIONS

PTSD = post-traumatic stress disorder
SARS = Severe Acute Respiratory Syndrome
WHO = World Health Organization

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Treatment and research lines for the patient with COVID-19. What do we have and where are we going?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents the most significant global public health crisis of this generation. From the beginning of the pandemic, several publications and on-line resources about different treatment lines have been done, and development effort in response to the COVID-19 pandemic to investigate potential therapies is unprecedented. Unfortunately, until now, there is not enough evidence to recommend any specific anti-COVID19 treatment. Randomized clinical trials and high-quality evidence, even in the middle of a pandemic, are needed. We provide a review of the latest published literature on the therapeutic strategies and current investigational lines for SARS-CoV-2.

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INTRODUCTION

Since the first case reported by Coronavirus disease (COVID-19) in Wuhan (1) China at the end of 2019 (2) to April 27, 2020, there have been > 3 million cases around the World, being Spain the first country in Europe with more than 229,000 cases and 23,500 deaths (3). COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with the disease may have mild symptoms up to more severe in a few days, such as fever, dry cough, myalgia, fatigue, diarrhea, dyspnea, and pneumonia in X-ray. In patients with COVID-19 pneumonia, an immune-mediated "cytokine storm" with several pro-inflammatory agents (IL-6, IL-8, IL-1β, granulocyte-macrophage colony-stimulating factor, and reactive oxygen species) and chemokines (such as CCL2, CCL-5, IFNγ-induced protein 10 (IP-10), and CCL3) all contribute to the acute respiratory failure and acute respiratory distress syndrome (ARDS). Approximately 20 to 41% of hospitalized patients with pneumonia developed ARDS (1). Indeed, ARDS is the leading cause of death in patients infected with SARS-CoV or Middle East respiratory syndrome (MERS-CoV). In

a postmortem assessment of COVID-19 patients with severe ARDS, specimens of infected lungs demonstrated bilateral diffuse alveolar damage with edema, pneumocyte desquamation, and hyaline membrane formation (4).

From the beginning of the pandemic, several publications and on-line resources about different treatments lines have been done. Nevertheless, there is insufficient evidence to support the safety or efficacy of the treatments used for COVID-19 (5).

Our aim is to review the therapeutic strategies and current investigational lines for SARS-CoV-2.

EVIDENCE ACQUISITION

This article will review the current evidence regarding the major proposed treatments, or experimental for COVID-19. We conducted a literary, comprehensive English-language literature research for original and review articles using the PubMed and Clinical trials database until May 2020. We search for the following MeSH terms: "COVID-19", "SARS-CoV-2", "coronavirus", "2019-nCoV", "Treatment", "Immunotherapy", "monoclonal antibody", "vaccine", "interleukin", "Immunomodulation", "Cytokines", "clinical trial". We included papers containing information on patients or treatments being considered for and undergoing clinical trials.

EVIDENCE SYNTHESIS

Understanding SARS-CoV-2 virus:

The genome sequencing indicated that the SARS-CoV-2 is a RNA betacoronavirus (1). SARS-CoV-2 has five major protein regions for virus structure assembly and viral replication (6). The cellular entry of coronaviruses depends on the binding of the spike (S) protein to a specific cellular receptor and subsequent S protein priming by cellular proteases. (2). The spike is a transmembrane glycoprotein that plays a pivotal role in mediating viral infection through binding the host receptor (6). Similarly, to SARS-CoV, SARS-CoV-2 employs the angiotensin-converting enzyme 2 (ACE2) as a receptor for cellular entry (2). The binding affinity of the S protein and ACE2 was found to be a significant determinant of the SARS-CoV replication rate and disease severity (2). The viral entry also depends on a host type 2 transmembrane serine protease (TMPRSS2) that facilitates cell entry via the S protein (2, 7). Once inside the cell, viral polyproteins synthesized RNA via RNA polymerase, and they release the viral particles. (7). These viral mechanisms provide potential and promising drug targets, such as 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase. Additional drug targets include viral entry and immune regulation pathways (7). Table-1 summarizes the mechanism of action of select treatments or adjunctive therapies for COVID-19.

PHARMACOLOGICAL INTERVENTIONS IN COVID-19: WHAT WE HAVE?

COVID-19 viral infection is a life-threatening disease. There is insufficient evidence to support the safety or efficacy of the drugs used in COVID-19. Also, even some of the treatments used are under the support of clinical trials or compassionate use. Below, we reviewed the published clinical experiences of some of the most promising repurposed drugs for COVID-19.

Antimalarial: Are they useful and safe to treat COVID-19 patients?

Chloroquine and hydroxychloroquine are drugs used in the treatment of malaria, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (7). Also, it has been demonstrated to have an anti-SARS-CoV activity *in vitro* (8). Briefing news from China reported chloroquine was successfully used to treat a series of more than 100 COVID-19 cases improving lung imaging findings, promoting virus-free conversion, and reduced disease progression (7).

A review by Cortegiani et al. of six articles published in March 2020 on the efficacy and safety of chloroquine for COVID-19 treatment suggested there is sufficient preclinical evidence to justify clinical research on the topic and extrapolated the safety of chloroquine on its existing use in clinical practice for other indications (8). In an observational study by Gautret et al., 80 patients with confirmed COVID-19 were treated with hydroxychloroquine in combination with

Table 1 - Summarizes the mechanism of action of select treatments or adjunctive therapies for COVID-19.

Drugs/Agents	Target	Doses (adults)	Adverse events	Observations
Chloroquine and hidroxichloroquine	Blockade of viral entry and immunomodulatory effects through inhibition of cytokine production (both share the same mechanism).	500 mg by mouth every 12-24 hours for 5 or 7 days (500 mg of chloroquine phosphate [salt] = 300 mg chloroquine base).	Abdominal cramps, anorexia, diarrhea, nausea, vomiting, QTc prolongation, hemolysis in G6PD deficiency, hypoglycemia, retinal toxicity, neuropsychiatric, and central nervous system effects.	Creatinine clearance <10 mL/min administer 50% of the dose. Hepatic: No dose adjustments (use with caution).
Lopinavir/ritonavir	Inhibiting 3C-like protease (3CLpro).	400/100 mg by mouth every 12 hours for up to 5-10 days maximum (at the beginning of the symptoms, first 7-10 days).	Diarrhea, nausea, vomiting, hepatotoxicity, hypertriglyceridemia and hypercholesterolemia, anxiety, headache, myalgia, pancreatitis.	No kidney or hepatic dose adjustments recommended (use with caution in hepatic impairment).
Remdesivir	RNA polymerase inhibitor.	Loading dose 200 mg intravenous followed 100 mg intravenous of maintenance once daily from day 2 to 10.	The main side effect is hypotension due to infusion. Other possible adverse reactions are nausea, vomiting, diarrhea, constipation, and abdominal pain.	Not recommended if creatinine clearance <30 mL/min.
Tocilizumab	IL-6 inhibition- reduction in cytokine storm.	Dose adjustments by weight: - ≥ 75 kg 600 mg one dose. - < 75 kg 400 mg one dose. Second dose 8-12 hours after the first dose if inadequate response.	Increase in upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased AST, infusion-related reactions. Hematologic effects, infections, hepatotoxicity, gastrointestinal perforations, hypersensitivity reactions.	No dose adjustments recommended in mild or moderate kidney impairment. No hepatic dose adjustments recommended (not studied). Caution in patients with neutropenia (<500 cells/μL) or thrombocytopenia (<50 000/μL)
Metilprednisolone	Regulate a vast array of physiological processes, and synthetic derivatives of these molecules are widely used in the clinic for treating inflammatory disorders, autoimmune diseases.	40 to 80 mg / IV / day, without exceeding 2 mg / kg (maximum 5 days).	Most frequent Nausea, vomiting, heartburn, headache, dizziness, trouble sleeping, appetite changes, increased sweating, or acne may occur.	kidney or hepatic failure (caution).
Favipiravir	RNA polymerase inhibitor.	Doses vary based on indication; limited data available.	Hyperuricemia, diarrhea, elevated transaminases, reduction in neutrophil count.	No required kidney adjustment (limited data available). Dose adjustment in Child-Pugh C is recommended.
Anakinra	Antagonist of IL-1β. The inhibition of IL-1β reduces the cytokine storm caused by infection.	100 mg subcutaneous injection per day.	Diarrhea, fever or chills, headache, itching, pain, redness, swelling, tenderness or warmth on the skin, joint pain, muscle aches and pains, nausea or vomiting, runny nose or sneezing and sore throat.	Creatinine clearance <30 mL/min or terminal renal failure (dialysis included) administer 100% of de dose every other day. Severe hepatic failure (caution).

azithromycin for at least three days and, followed up for at least six days. The majority of patients (92%) in the study had a low degree of illness (National Early Warning Score (NEWS) 0 - 4). The authors reported that 81.3% of patients who had a favorable outcome were discharged and, 83% had a fall in nasopharyngeal viral load, testing negative on day seven (9) Despite its small sample size, hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients, and its effect is reinforced by azithromycin (9).

Also, studies of chloroquine prophylaxis in healthcare workers (NCT04303507) and hydroxychloroquine for post-exposure prophylaxis after high-risk exposures (NCT04308668) are planned or enrolling. However, all the commented studies have important limitations, including small sample size, limited long-term outcome follow-up, etc... (7).

A few data exist regarding the optimal dose to ensure safety and efficacy. However, the recommended treatment for hydroxychloroquine in COVID-19 disease is 400 mg twice daily for one day, followed by 200 mg twice daily for five or seven days. Further studies are needed to determine the adequate dose. These drugs are relatively well tolerated. However, studies have reported adverse events, such as QTc prolongation and potential arrhythmias, especially in combination with QT-interval prolonging medications such as azithromycin or fluoroquinolones (electrocardiography to evaluate prolonged QT is recommended). (7). Even United States President Trump publically advocated the use of hydroxychloroquine and azithromycin in COVID-19. (Following this event, news of chloroquine poisoning from inappropriate over the counter use of the medication, including a report of a fatality, have surfaced in the U.S. and Nigeria (10)). Borba et al. investigated high versus low dose chloroquine (NCT04323527) in 81 patients and found more patients in the high dose chloroquine arm presented with QTc >500 mms (25%) when compared to the lower dose arm. The mortality rate was 13.5% (95% CI 6.9 – 23%), and recruitment was halted early in this arm because of adverse events. (11). Other side effects reported are hypoglycemia, neuropsychiatric effects, retinopathy diarrhea, vomiting, abdominal pain, nausea, and rash or itch (12). The use of chloroquine and hydroxychloroquine in pregnancy is considered safe. (7).

There is lack of robust evidence to conclude about the effectiveness and safe of these drugs. However, ongoing clinical trials could determine the role of chloroquine and hydroxychloroquine in this disease.

Antivirals: Yes or Not? that is the question

Lopinavir/ritonavir is an oral drug approved for human immunodeficiency virus (HIV) treatment and is perhaps one of the most studied drugs. There is no published data for lopinavir/ritonavir *in vitro* activity for SARS-CoV-2 (7). Recent reports from Cao et al. comparing the efficacy of lopinavir/ritonavir vs standard care in adults hospitalized with severe COVID-19 found that this drugs did not have time for clinical improvement different from those patients assigned to standard of care alone in the intention-to-treat population (median, 16 days vs. 16 days; hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80; P=0.09). Also, it did not reduce mortality, or diminish throat viral RNA detectability in patients with serious COVID-19 (19.2% vs 25.0%: absolute difference, −5.8% [95% CI, −17.3% to 5.7%]) (13).

The Wuhan University Quick Guide for the treatment of patients with COVID-19 infection makes a weak recommendation in favor of the use of oral lopinavir/ritonavir, clarifying that if the window for treatment is lost, it is not longer effective, this guideline does not recommend other antivirals (10). The administration at the beginning of the symptoms (first 7-10 days) appears to be important, delayed therapy initiation with lopinavir/ritonavir did not affect clinical outcomes (7). Current data suggest a limited role for lopinavir/ritonavir in COVID-19 treatment.

The most used and studied lopinavir/ritonavir dosing regimen for COVID-19 treatment is 400mg/100mg twice daily for up to 14 days (13). A randomized controlled trial (RCT) showed nearly 50% of patients experienced an adverse event, and 14% of recipients were unable to complete the full 14-day course of administration (13). The ad-

verse effects included nausea and diarrhea, hepatotoxicity with elevated transaminases by combination therapy, or viral infection in approximately 20% to 30% of patients (10).

- Remdesivir formally known as GS-5734 (a nucleotide analog prodrug that inhibits viral RNA polymerases who has demonstrated activity against SARS-CoV-2 *in vitro*) has shown improvement in oxygen-support status in 68% of patients, mortality rate was 13% over a median follow-up of 18 days (14). The interpretation of the results of this study is limited. Clinical trials are ongoing to evaluate the safety and antiviral activity of Remdesivir in COVID-19 (NCT04292899, NCT04292730, NCT04257656, NCT04252664, NCT04280705).
- Ribavirin: Its activity against other coronaviruses makes it a candidate for COVID-19 treatment. However, its *in vitro* activity against SARS-CoV was limited and required high concentrations to inhibit viral replication and combination therapy (7). It can cause severe adverse events such as hemolytic anemia reported in more than 60% of patients in SARS trial with a high dose (7). Other adverse events reported diarrhea, nausea, stomatitis, and transaminase elevations (15). Ribavirin is also a known teratogen and contraindicated in pregnancy (7).
- Favipiravir (T-705 - the active agent inhibits the RNA polymerase, halting viral replication). In an open-label clinical trial involving two treatment arms in patients with SARS-CoV-2 (favipiravir and lopinavir/ritonavir), the favipiravir arm performed better than the reference arm in terms of disease progression and clearance values (16). High doses should be considered for COVID-19. A loading dose of 2400mg to 3000mg every 12 hours by two doses, followed by a maintenance dose (1200mg to 1800mg every 12 hours). In general, the drug is well-tolerated, although the adverse event profile for higher-dose regimens is limited (7). (NCT04346628 NCT04359615; NCT04336904; NCT04349241; NCT04358549; NCT04303299; NCT04310228; NCT04333589).
- Oseltamivir (a neuraminidase inhibitor approved for the treatment of influenza) has no documented *in vitro* activity against SARS-CoV2) and has no role in the management of COVID-19 once the disease has been excluded (7).
- Umifenovir (also known as Arbidol, unavailable in Spain) has a mechanism of action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope. The current dose of 200mg orally every 8 hours for influenza is being studied for COVID-19 treatment (7). Several clinical trials are ongoing, on monotherapy (NCT04260594) or in combination (NCT04252885, NCT04273763, NCT04261907, NCT04286503, NCT04350684, NCT04323345, NCT04333589) (16).

Monoclonal antibodies:

- **Tocilizumab** (IL-6 receptor antagonist) has been used in a small series of severe COVID-19 cases with success early reports (7). IL-6 levels increase significantly in patients with severe COVID-19 (16). A report of 21 patients with COVID-19 showed that tocilizumab treatment, 400mg, was associated with clinical improvement in 91% of patients, measured by improved respiratory function, and successful discharge (7). For patients with reduced efficacy of the first dose, additional treatment can be applied after 12 hours (the prescription is the same as before), with a maximum of two cumulative doses (16). Tocilizumab is included in several RCT in Europe and United States (NCT04356937 NCT04346355, NCT04345445, NCT04331795, NCT04317092, NCT04320615, NCT04361552, NCT04332094, NCT04320615).
- **Anakinra:** (antagonist of IL-1β) the inhibition of IL-1β reduces the cytokine storm caused by infection. Data from a phase 3 randomized controlled trial of Anakinra IL-1 blockade in sepsis with Macrophage

Activation Syndrome (MAS) characteristics showed a significant improvement in the 28-day survival rate (65.4% Anakinra vs. 35.3% placebo), with HR of fatal outcome of 0.28 (0.11–0.71, p = 0.0071), with no increased adverse events. Thus, anakinra could have a potential use to reduce systemic inflammation and lung damage caused by SARS-CoV2, although, to date this is not evidenced in clinical trials. (17) (NCT04364009, NCT04366232, NCT04362943, NCT04357366, NCT04324021, NCT04341584, NCT04362111, NCT04330638).

Corticosteroids:

Corticosteroids have anti-inflammatory functions. The inhibition of excessive inflammation through the timely administration of glucocorticoids in the early stage of inflammatory cytokine storm effectively prevents the occurrence of ARDS (15). A recent retrospective study of 201 patients with COVID-19 in China found that, for those who developed ARDS, treatment with methylprednisolone was associated with a decreased risk of death (23/50 [46%] with steroids vs. 21/34 [62%] without; HR, 0.38 [95% CI,0.20-0.72]) (15). For patients with progressive deterioration of oxygenation indicators, rapid imaging progression or an excessive inflammatory response, the use of glucocorticoid in the short term (3–5 days) is appropriate, and the recommended dose is no more than the equivalent to methylprednisolone 1–2 mg/kg/day (15).

Melatonin:

Melatonin (N-acetyl-5-methoxytryptamine) is used to treat sleep disorders, delirium, atherosclerosis, respiratory disease, and viral infections (4). It is not viricidal, but it has indirect anti-viral actions due to its anti-inflammation, anti-oxidation, and immune-enhancing features (4). In previous respiratory syncytial virus models, melatonin caused downregulation of acute lung oxidative injury, pro-inflammatory cytokine release, and inflammatory cell recruitment (4). Indeed, melatonin indirectly regulates ACE2 expression, a key entry receptor involved in viral infection of human coronavirus, including SARS-CoV-2 (6). A recent meta-analysis of a total of 22 randomized controlled trials suggested that a supplementary use of melatonin is associated with a significant reduction of TNF-α and IL-6 level (18). In another trial of patients who have severe multiple sclerosis, orally 25 mg/d of melatonin for six months promoted a significant reduction in serum concentrations of TNF-α, IL-6, IL-1β, and lipoperoxides (19). These findings support a rationale for melatonin use in viral diseases as a supplement, reducing the levels of circulating cytokines and pro-inflammatory cytokine levels in COVID-19 patients. Studies suggest that the use of melatonin is safe and well-tolerated (6). The adverse effects are limited to occasional dizziness, headache, nausea, and sleepiness (6). However, the direct evidence of melatonin application in COVID-19 is unclear. A clinical trial is ongoing to evaluate the efficacy of melatonin in the prophylaxis of COVID-19 among healthcare workers (NCT04353128).

Miscellaneous agents or new lines of treatment to investigate?

Other drugs have demonstrated *in vitro* activity or have mechanisms purposed to inhibit SARS-CoV-2, including, baricitinib, imatinib, dasatinib, and cyclosporine (7). Current Chinese guidelines list interferons as an alternative for combination therapy (7). In one of the systematic reviews included, they report that interferon alone or in combination with ribavirin, lopinavir/ritonavir, has shown antiviral activity against coronavirus in studies extrapolated from SARS, Middle East respiratory syndrome coronavirus (MERS--CoV) and some reports from COVID-19 (6).

Research efforts directed towards the design and development of vaccines for SARS--CoV-2 are increasing, and some related analyses are already being reported in distinct, parallel studies (20). Most COVID-19 vaccine private/industry developers are in North America followed by China, Asia (excluding China), Australia, and Europe. (21). Given the close genetic similarity between the structural proteins of SARS-CoV and SARS--CoV-2, immunological studies of the structural proteins of SARS-CoV could potentially aid the

vaccine development for SARS-CoV-2. Focused specifically on the S and N proteins as these are known to induce potent and long-lived immune responses in SARS-CoV (20). About hyperimmune gammaglobulin and convalescent plasma from recovered patients can be a complementary therapy for COVID-19, but there is no evidence to recommend their use (7,15). Unfortunately, until now there is no current evidence to recommend any specific anti-COVID19 treatment (7).

CONCLUSIONS

Since the COVID-19 outbreak has begun, the global research and development effort in response to the COVID-19 pandemic to investigate potential therapies is unprecedented. Indeed, the volume and quick pace of published literature is continually changing. However, despite all the efforts done, no treatments have been shown effectiveness to date and randomized controlled clinical trials with high-quality evidence even in the middle of a pandemic are needed.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The effect of the Covid-19 Pandemic on pediatric urology

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ABSTRACT

Medical and surgical priorities have changed dramatically at the time of this pandemic. Scientific societies around the World have provided rapid guidance, underpinned by the best knowledge available, on the adaptation of their guidelines recommendations to the current situation. There are very limited scientific evidence especially in our subspecialty of pediatric urology. We carry out a review of the little scientific evidence based mainly on the few publications available to date and on the recommendations of the main scientific societies regarding which patients should undergo surgery, when surgery should be performed and how patient visits should be organize.

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INTRODUCTION

Since the COVID-19 epidemic was first declared in China in December 2019 (1), the virus has spread rapidly around the World owing to its characteristics: rapid spread, high contagiousness, and mortality from viral pneumonia. Critically, hospitals in many countries have had to transform. In Europe as of April 28, there have been 880,000 cases of COVID-19, and specifically in Spain 213,000 cases have been confirmed by Polymerase Chain Reaction (PCR) (2). We have had to convert the departments of our hospitals in an attempt to ensure that human resources and medical infrastructure were adequate to treat patients affected by COVID-19, and a key element of these efforts has been an increase in staff levels through the involvement of doctors from different specialties in the care of these patients. As our healthcare system has become increasingly saturated, most nurses have been moved to COVID-19 areas and the majority of the OR personnel have been

moved to the ICU owing to the rise in the need for ventilated beds; these changes have entailed the added difficulty of obtaining adequate personal protective equipment (PPE). Other specialized hospitals have been declared COVID-19 free in order to allow treatment of all patients considered non-infected. Pregnant COVID-19 patients have been transferred to these centers, and all cases of pediatric disease are being treated exclusively in maternal and pediatric hospitals. The COVID-19 crisis has forced health care providers to establish priorities for the treatment of pathologies and to suspend elective surgeries, all with the aim of increasing the number of personnel, and this, too, has meant an involuntary change in our health care systems (3). The decision on which type of care should be postponed and which should continue will need to be reviewed as the pandemic situation changes.

Medical and surgical societies around the World have provided rapid guidance, underpinned by the best knowledge available, on the adaptation of their guidelines recommendations to the current situation (4). But we must also ask ourselves what strategy to follow for those COVID-19 patients who require surgical interventions, bearing in mind the very limited scientific evidence currently available, especially in our subspecialty of pediatric urology.

Here, we carry out a review of the scant scientific evidence based mainly on the few publications available to date and on the recommendations of the main scientific societies regarding which patients should undergo surgery, when surgery should be performed, how patient visits should be organized, which risks need to be addressed, which surgical techniques are safer in this pandemic, how we should protect ourselves, and what risks a child faces when undergoing an operation affected by COVID-19.

SPECIAL CONSIDERATIONS IN CHILDREN PEDIATRIC PATIENTS, COVID-19 INFECTION, AND COMORBIDITIES

The rapid spread of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic, with infection of individuals of all ages residing in almost every country in the World (5). The pediatric population appears to be affected in much smaller proportions than adults, with only 2% of cases described in patients under age 20. According to data published by the Chinese Center for Disease Control and Prevention, only 1% of cases occur in those aged between 10 and 19 years and 1% in children under 10 years old (6).

An epidemiologic report described 731 confirmed COVID-19 cases in the pediatric population, with over 90% of patients characterized as asymptomatic or as having mild or moderate symptoms (7). In more severe cases, symptoms can include gastrointestinal symptoms and patients can progress to respiratory failure, shock, coagulation dysfunction, renal damage, septic shock, and multiorgan failure. A case of Kawasaki disease with concurrent COVID-19 infection has recently been published in the literature (8), and cutaneous manifestations of COVID-19 have also been reported in children (9).

As we know, at the moment there is no specific treatment. Symptomatic treatment is administered in mild and moderate cases, with supportive measures and/or treatment of complications in severe cases. Numerous controlled clinical trials with newly developed molecules and drugs already authorized for other indications have been launched for complicated cases, primarily within hospitals (10).

In Spain, the above-described trend continued in April: as of 3 April there were 111 confirmed cases in children under 2 years of age (0.2%), 39 in children aged between 2 and 4 years (0.1%), and 193 in children aged between 5 and 14 years (0.3%). Data were extracted from 54% of the reported cases (63,002 cases) as of that date (117,710 cases) (11). Based on the currently available data, children with COVID-19 have a better prognosis than adults, with few reported severe cases, and in mild cases recovery occurs within 1–2 weeks of disease onset. Most of the confirmed cases were secondary to exposure to family contacts. However, transmission from children to adults and other children can occur, as documented in a number of pediatric cases in China. On the other hand, it has

been reported that the elimination of the virus in respiratory secretions and feces occurs over a longer period in children with mild symptoms than in adults, a fact that represents a great challenge for infection control (12). Transmission of the virus from asymptomatic children and a carrier period of up to 21 days have also been demonstrated. These data may explain a greater number of infections. Therefore, children should participate in the usual preventive actions to contain spread of the infection, and the protection of health professionals during evaluation and examination of children with respiratory infections is crucial (11).

While most cases of COVID-19 in children are not severe, there is a population with higher risk factors for poor disease course (Table-1) (9). One of the questions frequently asked by our urological pediatric patients or parents is whether they are at higher risk of suffering from COVID-19 due to their congenital urological diseases the fact that up to now there is no scientific evidence that congenital uropathy is a risk factor for poor evolution for the development of complications in patients with SARS-COVID-2.

When a patient is admitted to our pediatric urology unit and we suspect COVID-19 due to fever or suggestive symptoms, we carry out the PCR test with a pharyngeal sample to rule it out, as well as blood tests (hemogram, coagulation, venous blood gas, biochemistry with LDH, PCR, and PCT) and chest radiography (ideally portable). The use of chest ultrasound should be considered if it is available and if trained personnel are available to perform it. A single family member or other companion authorized by the parents must remain with the patient at all times, complying with the recommended isolation measures (surgical mask, gown, and frequent hand washing). It is recommended that the companion always be the same. In patients with severe disease, measurement of CPK, troponin, BNP, fibrinogen, D-dimer, and ferritin levels is recommended, as well as the acquisition of other data on hemophagocytic lympho-histiocytosis. Need for lumbar puncture will be assessed if neurological symptoms arise. Indication for other complementary tests will be evaluated according to the circumstances in each case.

SPECIAL CONSIDERATIONS IN THE SELECTION OF CARE FOR UROPEDIATRIC PATIENTS

Scientific societies for urology, such as the European Association of Urology (EAU) and the American Urological Association (AUA) (13), have created their own information centers for COVID-19 where they can be consulted.

The American College of Surgeons has established basic principles for clinical practice during this period. They recommend minimization of exposure to the hospital environment, with the following guiding principles:

- The goal is to provide timely surgical care to children with emergent and urgent pediatric surgical issues while optimizing patient care resources (e.g., hospital and intensive care unit beds, personal protective equipment, ventilators) and preserving the health of caregivers.
- There is no substitute for sound surgical judgment.
- Surgery should be performed only if delaying the procedure is likely to prolong hospital stay, increase the likelihood of later hospital admission, or cause harm to the patient.
- Children who have failed attempts at medical management of a surgical condition should be considered for surgery to decrease the future use of resources (e.g., recurrent infections in a branchial cleft cyst following a course of antibiotics).
- Shared multidisciplinary decisions regarding surgical scheduling should be made in the context of available institutional resources that will be variable and rapidly evolving.
- Telemedicine and teleconsultation services should be used for patient and physician interaction when available. For this, the creation of local review committees for decision-making related to COVID-19 surgical triage is very important (14).

1 - Groups of children at higher risk for poor disease course (Spanish Association of Pediatrics).

Immunosuppressed child	Primary immunodeficiencies (1) Solid organ transplant and hematopoietic progenitor transplantation Treatment with chemotherapy, immunosuppressants, or biological drugs Poorly controlled HIV (detectable CV, CD4 decrease, or CD4/CD8 inversion ratio)
Heart disease	With hemodynamic repercussions With requirement for medical treatment Pulmonary hypertension On transplant waiting list Recent surgery or catheterization
Chronic respiratory pathology (chronic lung diseases)	Cystic fibrosis Bronchopulmonary dysplasia Severe asthma Under tracheostomy, oxygen therapy, or home mechanical ventilation
Others	Dialysis Sickle cell disease Type 1 diabetes mellitus with poor metabolic control Severe malnutrition, short bowel, epidermolysis bullosa, severe encephalopathies, myopathies, inborn errors of metabolism, etc.

URGENT AND ELECTIVE SURGERIES

When the term "urgent surgery" is applied in the specialty of urology, and specifically in adult patients, one most commonly thinks of surgeries for oncological conditions or obstructive urolithiasis with risk of sepsis, which are much less frequent in children. On the other hand, within pediatric urology, one might think of testicular torsions as requiring urgent surgery, or of Wilms tumors, but these are much less frequent than the indications in adults. Most of our patients have congenital pathologies, and in our day-to--day practice we perform mostly reconstructive surgeries, although we can also treat obstructive lithiasis or pathologies involving risk of loss of kidney function. Prioritizing what is urgent or "elective" in this context may be more difficult than in adults. Due to these problems, European societies such as British Association of Pediatrics Urologist (BAPU) and the EAU/ESPU have published recommendations for pediatric urological procedures (Table-2) (4).

EAU/ESPU Recommendations

Panels were asked to provide tables with recommendations based on the level of priority, including those that the panels felt were critical drivers of outcome and would especially be impacted by the current crisis, and always based on the highest level of evidence that was possible.

LOW PRIORITY: Clinical harm (very unlikely if postponed for 6 months).

INTERMEDIATE PRIORITY: Cancel procedure but reconsider if there is an increase in capacity (postponement for more than 3 months not recommended: clinical harm possible but unlikely if the procedure is postponed for more than 3 months).

HIGH PRIORITY: The last procedure to be cancelled; prevent delay of >6 weeks. Clinical harm (e.g., loss of organ function) very likely if the procedure is postponed for >6 weeks).

EMERGENCY: Cannot be postponed more than 24 hours. Life-threatening/organ function-threatening condition.

The BAPU also recommends that routine surgery be discontinued. Emergency surgery should be limited to category 4 or 5, unless local capacity is good enough to allow category 3 to be considered (15).

ROUTINE PREOPERATIVE PCR IN CHILDREN

Is PCR recommended in all children before any surgery?

The EAU/ESPU guidelines recommend performing PCR for the COVID-19 test prior to any surgical intervention whenever possible (16). Nasopharyngeal swab with RT-PCR performed within 48 h preoperatively for the detection of COVID-19 unfortunately shows a false negative rate of 30%–40% (17); however, it is always useful (18). If it cannot be performed or the test result is unknown, the patient is to be treated as positive and the number of personnel present in the operating room limited in order to reduce risks. Unfortunately, the literature regarding the effect of surgery on susceptibility to COVID-19 is very limited and relates only to adults. In one study, the mean age of 34 patients who underwent elective surgeries (levels 3 and 4) during the incubation period of COVID-19 was 55 years. All patients developed COVID-19 pneumonia shortly after surgery; 44.1% of the patients required admission to ICU during disease progression and 20.5% died after admission to ICU (19).

Regional or local anesthesia should be considered whenever possible to prevent the need for mechanical ventilation, although local anesthesia is very rare in children compared with adults (11).

Risk of contagion in operating room situations

We know that certain procedures in the operating room generate aerosols (aerosol-generating procedures, AGP) and thereby increase the risk for surgical personnel if the patient is infected or in the incubation period (13). These include intubation, extubation, bronchoscopy, the introduction of chest tubes, electrocautery, and the use of ultrasonic devices. AGP should only be performed with full PPE, including an N95 mask or a powered air-purifying respirator (PAPR) designed for the operating room. It is advisable to use suction devices as much as possible.

Laparoscopic/robotic/open surgical techniques

The European Association for Endoscopic Surgery reports that there is very little scientific evidence on the relative risks of minimally invasive surgery versus conventional open surgery in the context of COVID-19. However, it recommends that the risk of viral contamination of personnel during surgery, whether open, laparoscopic, or robotic, be considered and that protective measures be used strictly to ensure the safety of operating room personnel and to maintain a functioning workforce. For minimally invasive procedures, the use of devices to filter released CO2 for aerosol particles should be considered (20). While insufficient data are available to recommend for or against an open approach versus a laparoscopic/robotic approach, the surgical team must choose an approach that minimizes operating time and maximizes safety for both patients and staff (21).

In the Chinese experience, 3,387 healthcare workers were infected with COVID-19 with a mortality of 0.6%. In this setting, special caution is mandatory to reduce the infection among healthcare workers caring for COVID-19 patients. The EAU Robotic Urology Section (ERUS) has developed guidelines for robotic surgery during the COVID-19 emergency. In the case of nondeferrable surgery, the release of surgical smoke during laparoscopic procedures may carry small viral particles. As a consequence, any laparoscopic or robotic surgery should be performed only when necessary. It may be of particular importance to perform robotic surgery at the lowest permissible intraabdominal pressure (22).

As reported by Zheng et al. (23), ultrasonic scalpels or the electrical equipment commonly used in minimally invasive surgery can easily produce large amounts of surgical smoke, and in particular, the low-temperature aerosol from ultrasonic scalpels or scissors cannot effectively deactivate the cellular components

Table 2 - Recommendations from the EAU/ESPU Paediatric Urology Guidelines Panel applicable during the COVID-19 pandemic.

Priority category	Low priority	Intermediate priority	High priority	Emergency
Definition	Clinical harm very unlikely if postponed 6 months	Clinical harm possible if postponed 3–4 months but unlikely	Clinical harm very likely if postponed >6 weeks.	Life-threatening situation
COVID recommendation	Benign scrotal and penile pathology, incontinence.	Semiurgent cases like initial postoperative ultrasound after upper tract surgery.	Urgent cases in which delay may cause irreversible progression or organ damage: includes ultrasound, VCUG in suspected severely obstructed uropathy where surgery is still considered.	Continue all care in which delay is potentially organ threatening or life threatening.
Postoperative follow -up schedule after surgery				
Priority category	Low priority	Intermediate priority	High priority	Emergency
Definition	Clinical harm very unlikely if postponed 6 months.	Clinical harm possible if postponed 3–4 months but unlikely.	Clinical harm very likely if postponed >6 weeks.	Life-threatening situation.
COVID recommendation	Follow-up by 6 months	Follow-up before end of 3 months	Follow-up within <6 weeks.	Follow-up within <24 hr.
	Orchidopexy, hydrocele, hypospadias, circumcision, inguinal hernia, buried penis, urolithiasis if no obstruction or infection.	Any kind of antireflux surgery, pyeloplasty, incontinence surgery if bladder emptying is working	Pyeloplasty with possible loss of function. Recurrent UTI after antireflux surgery. Incontinence surgery with bladder-emptying problems.	Macroscopic hematuria after trauma. Inguinal hernia repair with onset of scrotal pain. Suspected bowel obstruction or intestinal perforation in conjunction with bladder augmentation. Urolithiasis with signs of sepsis and/or obstruction. PUV with urinary retention. Local wound infection or abscess formation after any kind of surgery. Febrile UTI/uroseptical signs after any kind of surgery.
Surgical procedures for pediatric urology cases				
Priority category	Low priority	Intermediate priority	High priority	Emergency

Definition	Clinical harm very unlikely if postponed 6 months	Clinical harm possible if postponed 3–4 months but unlikely	Clinical harm very likely if postponed >6 weeks	Life-threatening situation
COVID recommendation	Defer by 6 months	Treat before end of 3 months Perform surgery that is semiurgent.	Treat within <6 weeks Perform surgery for urgent cases in which delay will cause irreversible progression of disease or organ damage.	Treat within <24 hr. Perform surgery in cases of organ-threatening or life-threatening disease.
	• Benign scrotal and penile surgery (orchidopexy, hydrocele, inguinal hernia, circumcision). • Functional surgery (incontinence surgery, meatotomy, botulinum toxin injections). • Genital reconstructive surgery (hypospadias, buried penis, other genital abnormalities). • Benign (hemi) nephrectomy. • Bladder augmentation, catheterizable stoma, appendicocecostomy due to the high and prolonged impact on patients and resources. • Bladder exstrophy correction depending on age and local situation.	• Surgery for VUR (open reimplant and bulk injection). • Pyeloplasty if no loss of function. • Urolithiasis if no infection or obstruction. • Botulinum toxin injections for neurogenic bladder only in selected cases.	• Pyeloplasty in UPJ obstruction with progressive loss of function or severe symptoms (consider drainage with JJ of nephrostomy). • PUV. • POM with progressive loss of function. • Urolithiasis with recurrent infections.	• Urosepsis with obstruction (urolithiasis, ureterocele with obstruction or POM). • Trauma with hemodynamic instability or urinoma formation. • PUV if urethral or suprapubic catheter cannot be placed. • Oncology (Wilms, malignant testicular/ paratesticular tumors, RMS of bladder and prostate, resection may be considered depending on local situation and condition of child). • Acute ischemia (testicular torsion – in neonates not exploring is an option due to low chance of salvaging testis, very low risk of metachronous contralateral torsion, and increased vulnerability of these patients). • Paraphimosis.

General considerations

- While most children themselves may not be severely ill with COVID-19, this pandemic will impact pediatric urological care. Careful decisions must be made on what care requires postponement and what care is essential to be continued.
- Depending on the resources and capacity we recommend to only treat high-priority and emergency cases surgically during the COVID-19 pandemic.
- Consider treating intermediate-priority patients if capacity is available, but not during the COVID-19 surge.
- It is important to note that postponing surgery in patients with obstructive uropathy (UPJ, UVJ obstruction, PUV, neurogenic bladder) may lead to loss of renal function and the decision to postpone may be revised depending on the duration of the local situation as well as the severity of the obstruction in the individual case. Temporary drainage methods may be considered to bridge definitive surgery.
- Undoubtedly there will be cases of congenital abnormalities where the optimal surgical time point will be surpassed, such as hypospadias and cryptorchidism. These children may be at risk for suboptimal outcome or increased psychological burden due to delayed surgery and should be prioritized in the long waiting list.

Abbreviations: **PUV** = posterior urethral valves; **POM** = primary obstructive megaureter; **UPJ** = ureteropelvic junction; **VCUG** = voiding cystourethrogram; **VUR** = vesicoureteral reflux; **UVJ =** ureterovesical junction; **and UTI** = urinary tract infection.

of the virus in patients. These authors concluded that the particle concentration of the smoke in laparoscopic surgery is significantly higher than that in traditional open surgery (23, 24). Thus, it is recommended that lower electrocautery power settings be used as much as possible.

It is mandatory to confirm the complete and correct deflation of the pneumoperitoneum at the end of the procedure. In fact, due to the low gas mobility in the pneumoperitoneum, the aerosol formed during the operation tends to concentrate in the abdominal cavity. Sudden release of trocar valves, non-airtight exchange of instruments, or even small abdominal extraction incisions can potentially expose the health care team to the pneumoperitoneum aerosol. Therefore, CO2 should be aspirated as much as possible before removing trocars. In order to minimize the use of the operating room and optimize the use of surgical resources, procedures must be performed by experienced surgeons (20).

Endoscopic procedures

Only one report in the literature has demonstrated the presence of SARS-COV-2 in urine specimens, in 6.9% of patients, and there is no available evidence on urine transmission (26). It is recommended that endoscopic procedures and urethral catheterization be performed with caution and that surgeons should be completely protected against infection if the patient has suspected or confirmed COVID-19.

OUTPATIENTS AND TELEMEDICINE

To date, no specific treatment is available for COVID-19 infection and it is generally accepted that social distancing is the main and perhaps the only measure to prevent or contain the spread of infection so that the number of critical cases does not dramatically exceed the resources of a health system at risk of collapse. Reduction in outpatient clinic visits during various stages of severity of the COVID-19 pandemic is recommended. Pediatric urology telemedicine can lead to fewer patient contacts, lower infection rates among staff, and continuation of pediatric urological care by quarantined urologists. However, the proportion of patients eligible for telemedicine, their wish to use telemedicine, and their demographic risk profile for acquiring a severe pandemic infection are unknown. The ESPU has provided guidance on the reduction of outpatient clinic visits during the various stages of severity of the COVID-19 pandemic:

- **Stage 1:** Start to reduce outpatient cases such as benign scrotal and penile pathology as well as incontinence.
- **Stage 2:** See only cases that are at least semi urgent, such as those requiring initial postoperative ultrasound after upper tract reconstruction. Consider postponing prolonged (postoperative) follow-up in stable patients.
- **Stage 3:** Continue care for urgent cases in which delay may cause irreversible progression of disease or organ damage. This includes ultrasound and voiding cystography in suspected severely obstructive uropathy in which surgery is still considered.
- **Stage 4:** Continue all care for cases in which a delay of care is potentially organ-threatening or life-threatening.

In the case of postoperative follow-up of patients with genitourinary pathologies, it is advisable to carry out the follow-up by sending photographic documentation in compliance with the General Data Protection Regulation (GDPR). If the visit has to be in person, the patient should be accompanied by a single caregiver (14). A distance of 2 m should be maintained between patients. Every child with suspected respiratory infection should wear a mask. Children under one year of age must be kept in their strollers and in baby seats or restraint systems and away from other patients. In pediatric waiting rooms, there will be no materials such as toys, books, or other objects that children can

share and that cannot guarantee that recommended material hygiene and cleanliness standards are met, in addition to evidence of transmission before the manifestation of symptoms. If there are COVID-19 symptoms, the child or caregiver has tested positive for COVID-19, or they are in quarantine, they should be seen in a COVID-dedicated area of the hospital without interaction with other patients (8).

TRAINING PROGRAMS

All interhospital staff movements with residents training in other hospitals and all undergraduate clinical rounds have been canceled. All training programs for residents as well as fellowship programs in pediatric urology in Spain have been affected. Many residents have had to become so-called front-line doctors caring for patients affected by COVID-19. It is recommended that all procedures are performed by experienced urologists confident in the procedure. Procedures should be performed with the minimum number of staff members, who should also be fully trained and experienced. Furthermore, no external observers (i.e., fellows or students) should be present during procedures until the pandemic has been controlled, which we hope will be in the approaching period (22). Currently, training meetings held between companies or for the same department are scheduled via telematics.

INCREASING SURGICAL ACTIVITY AFTER THE PANDEMIC IS OVER

There is no existing knowledge on the adverse impacts of loss of surgical capacity on patients' surgical condition and associated health or on prognosis. A new model will have to be established after the pandemic based on the length of the surgical waiting list.

WHAT ABOUT LATIN AMERICA? WHAT HAVE THEY LEARNED FROM EUROPE'S EXPERIENCE?

Countries in Latin America are following the programs applied in Europe because the European countries have more experience with COVID-19. In preparation for potential surges in cases of COVID-19, most governments have chosen to create new healthcare facilities and have emphasized the need for careful planning around elective procedures, taking into account multiple considerations such as adequacy of supplies of PPE and other essential equipment, testing capacity, sanitation protocols, and workforce availability. Hospitals need to maintain adequate staffing levels to cover a potential surge in COVID-19 cases and should have enough beds, PPE, ventilators, and trained staff to allow these surgeries to take place without resorting to a crisis standard of care.

Elective surgeries were initially suspended to preserve hospital bed capacity and PPE. When the data indicate a better position regarding hospital capacity, and provided individual institutions can accommodate their internal demand for PPE, it may be time to start performing some of these procedures again.

As in many countries, training programs have continued through societies, webinars, and virtual masterclasses.

Across Latin America, and indeed in all developing countries facing the COVID-19 pandemic, there are many unanswered key questions relating to impacts on the economy, levels of poverty, social and psychological problems, crime post quarantine, etc. No nation is prepared to face this crisis, but in developing countries the problem is even worse because they are all constantly in a state of crisis. In this context the post-COVID-19 era represents a huge challenge.

CONCLUSIONS

The COVID-19 virus has been impacting dramatically on the normal life of the departments. Because of the necessity to adopt strategies to contain the diffusion, all surgical departments have to be restricted. Perform surgery only in cases of organ-threatening or life-threatening disease. Suggested reduction in outpatient clinic visits during various stages of severity of the COVID-19 pandemic.

SUMMARY OF RECOMMENDATIONS

- Consider treating only high-priority and emergency cases surgically during the COVID pandemic.
- Consider treating intermediate-priority patients if capacity is available but not during the COVID surge.
- Non-surgical management should be considered, to begin with, including medical treatment (e.g. antibiotics for vesico-ureteral reflux associated urinary tract infections), endovascular embolization (e.g. for bleeding renal traumas), or urinary tract diversion.
- Perform PCR for the COVID-19 test prior to any surgical intervention whenever possible.
- Follow the local recommendations for personal protective equipment (PPE).
- Avoid or reduce the use of monopolar electrosurgery, ultrasonic dissectors, and advanced bipolar devices, as these can lead to particle aerosolization.
- All minimally invasive procedures should preferably be performed by experienced surgeons.
- It is recommended that electrocautery power setting be lowered as much as possible in order to reduce the surgical smoke production, especially in laparoscopic surgery. During access, electrocautery should be provided with automatic suction system.
- Reduction in outpatient clinic visits during various stages of severity of the COVID-19 pandemic is recommended
- Multidisciplinary team meetings are recommended to offer the optimum therapeutics.
- Regional or local anesthesia should be considered whenever possible to prevent the need for mechanical ventilation.

ABBREVIATIONS

PCR = Polymerase Chain Reaction
BAPU = British Association of Pediatrics Urologist
PPE = Personal Protective Equipment

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Early experience with COVID-19 in kidney transplantation recipients: update and review

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ABSTRACT

Introduction: little is known on the risk factors, clinical presentation, therapeutic protocols, and outcomes of kidney transplantation recipients (KTRs) who become infected by SARS-CoV-2.
Purpose: to provide an updated view regarding the early experience obtained from the management of KTRs with COVID-19.
Materials and Methods: A narrative review was conducted using PubMed database to identify relevant articles written in English/Spanish, and published through May 15, 2020. Search terms included: "coronavirus", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "COVID-19", "COVID", "renal transplantation", and "kidney transplantation". Case series were considered eligible, and case reports excluded. Thirty-four articles were included in the review.
Results: KTRs should be considered immunocompromised hosts: potential risk for infection, non-negligible comorbidity, and exposure to long-term immunosuppression. Only single center small retrospective experiences are still available regarding KTRs with COVID-19. SARS-CoV-2 symptoms in KTRs are similar to that observed for the general population, being fever and cough the most frequently observed. Mild-to-moderate symptomatic KTRs can be managed in an outpatient setting, while patients exhibiting severe symptoms must be addmited to hospital. More rapid clinical progression, and higher complication and death rates have been observed for hospitalized KTRs, requiring hemodyalisis or ventilatory support. Lymphopenia, elevated serum markers (C-reactive protein, procalcitonin, IL-6, D-dimer), and chest-X-ray findings consistent with pneumonia are linked to worse prognosis. A number of antiviral therapies have been used. However, it is difficult to draw meaningful conclusions regarding their efficacy at this point. Baseline immunosupression regimen should be adjusted in a case-by-case manner. However, it poses a significant challenge.

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INTRODUCTION

Since december 2019, a growing number of atypical pneumonia cases of unknown origin were initially detected in different medical centers of Wuhan (Hubei, China). The infection spread rapidly across the World causing a global pandemic in only three months (1). The analysis of the genome sequence of specimens retrieved from the respiratory tract of those patients, revealed a single-stranded and positive-sense RNA virus as etiological agent. This virus share close similarities in its structure with the severe respiratory syndrome coronavirus (SARS-CoV) that cause the SARS global pandemic in 2003, and the Middle East respiratory syndrome (MERS) epidemic in 2012 (MERS-CoV) (2-4). The novel coronavirus was so-called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Comitee on Taxonomy of Viruses. The disease produced by SARS-CoV-2 was named Coronavirus Disease 2019 (COVID-19) by World Health Organization (5), after declaring it a potentially lethal infectious disease posing a real threat to global health security, as evidenced by a dramatic total of 4,466,944 new cases, and 299,507 deaths by May 15th, 2020 since the beginning of the pandemic worldwide (6).

Although the clinical debut resembles that produced by other common respiratory viruses, the course may evolve to a potentially life-threatening respiratory distress, multi-organ failure, or even death in a short time frame. The infection may cause other disorders affecting mainly the gastrointestinal and nervous systems. It has been reported to affect more severely to older patients, and those exhibiting a number of comorbid conditions including hypertension (6%), diabetes (7.3%), immunosuppresion, lung or cardiac insufficiency (10.5%), chronic kidney disease (CKD), cancer (5.6%), and renal replacement therapy (RRT) (7).

Kidney transplantation recipients (KTRs) should be considered immunocompromised hosts for their unique potential risk for COVID-19 infection, given their non-negligible comorbidity, exposure to long-term immunosuppression, and residual CKD. In fact, the SARS pandemic was reported to affect KTRs (8), and various solid organ transplantation recipients died in both SARS and MERS epidemics (9, 10). However, to date little is known on the risk factors, clinical presentation, diagnostic troubles, therapeutic protocols, and outcomes of KTRs who become infected by SARS--CoV-2. The aim of this review is to provide an updated view regarding the early experience obtained from their management.

MATERIALS AND METHODS

A literature review was conducted using PubMed database to identify relevant articles written in English or Spanish, and published through May 15, 2020. Search terms included "coronavirus", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "COVID-19", "COVID", "renal transplantation", and "kidney transplantation". Due to the lack of randomized controlled trials, case series were considered eligible for inclusion. Case reports were excluded. The initial search provided 45 articles, which abstracts were independently reviewed. Finally, 34 articles reporting on KTRs with SARS-CoV-2 infection were reviewed.

Comorbid conditions and treatment

KTRs are at a higher risk to COVID-19 infection due to immunosuppression, underlying CKD, and other comorbid conditions, in particular hypertension (HTN) and diabetes (DM) (11). However, important comorbidity is inherent to CKD and RRT, thus being quite common in a KTR. Table-1 includes the most representative series reviewed (9 series; N=184 patients), summarizing all the relevant information regarding demographics, transplantation, manteinance immunosuppression regimen, and comorbid conditions of the patients included. Most of these patients (15-94%) exhibited at least one comorbid condition such as HTN (40-100%), DM (15-69%), active cancer (3-20%), and chronic heart or lung disease (15-42%).

They were receiving a number of medications for comorbidity control (i.e., mainly a wide variety of antihypertensives, antidiabetics, and statins). It has been hypothesized that SARS--CoV-2 uses angiotensin-converting enzyme 2

Table 1. Summary of demographics, comorbid conditions, time from transplantation, source of donation, and baseline immunossuppression regimen.

Author	#Number of patients	Age range (yrs.)	Gender M/F (%)	Comorbid conditions (%)	Time from Transplant range (months)	Source of donation DD/ LD (%)	Baseline immunosuppression regime				
							Anti-Mb (%)	CNI (%)	m-TOR I (%)	GC (%)	AB (%)
Banerjee D, et al. (14)	7	45-69	57/43	HTN 85 DM 42 O: 42	1-360 (28% first 3 months)	100/0	100	85	0	71	0
Alberici, et al. (7)	20	41-73	80/20	HTN: 85 DM: 15 O: 15	108-240	N/A	70	95	10	65	0
CUKTP (1)	15	28-72	66/33	N/A	38-118	80/20	86	93	0	67	13
Zhang, et al. (24)	5	37-64	80/20	HTN:40 DM:20 Cancer:20	2-36	100/0	80	80	20	80	0
Pereira, et al. (16)	48 (2% kidney-pancreas, 2% liver-kidney)	46-68	53/47	HTN: 64 DM: 46 Cancer: 3 O: 20	35-127	N/A	76	86	7	59	3
Akalin, et al. (13)	36	32-77	72/28	HTN: 94 DM:69 O: 17	N/A	75/25	86	97	0	94	0
Zhu, et al. (15)	10	24-65	80/20	HTN: 50 O: 30	6-144	7/3	100	100	0	70	0
Montagud-Marrahi, et al. (18)	33 (6% kidney-pancreas)	40-74	58/42	N/A	48-180	N/A	62.5	87.8	42.4	78.8	0
Nair, et al. (23)	10	47-67	60/40	HTN: 100 DM: 90	N/A	50/50	100	90	10	70	6

CUKTP = Columbia University Kidney Transplant Program; **M** = male; **F** = female; **DD** = deceased donor; **L/D** = living donor; **Anti-Mb** = antimetabolite therapy; **CNI** = calcineurin inhibitors; **m-TOR I** = m-TOR inhibitors; **GC** = glucocorticoid therapy; **AB** = monoclonal/polyclonal antibodies; **HTN** = hypertension; **DM** = diabetes mellitus; **O** = others (including heart or lung chonic disease, HIV infection, HCV infection, CMV infection, and hemolytic anemia)

(ACE2) to gain entry in the cells, making ACE inhibitors and/or angiotensin receptor blockers (ARBs) increase the risk of SARS-CoV-2 pneumonia via altered expression of ACE2. There are no clinical data in favor or against this hypothesis, and changing the doses of ACE inhibitors/ARBs during the treatment of infection seems not recommended (12). Similarly, no recommendation is advised regarding the remaining concomitant therapy. It seems prudent keeping the current medication inaltered unless otherwise specified, and act in a case-by-case basis according to the situation exhibited by a particular patient.

COVID-19 infection

SARS-CoV-2 causes a variety of symptoms including upper respiratory (sore throat), lower respiratory (cough and dyspnea), constitutional (fever, malaise, myalgia), gastrointestinal (nausea, vomiting, abdominal pain, diarrhea), or a combi-

nation of them. Many patients have also reported anosmia or dysgeusia; somewhat a unique feature of this syndrome (13). COVID-19 symptoms were reported frequently among the patients included. Fever (58-100%) and cough (42-100%) were noted almost invariably, followed by diarrhea (20-90%), dyspnea (5-90%), fatigue or myalgia (5-90%), and coryza (10%), similar to that observed for the general population (Table-2). Interestingly, no neurologic symptoms were recorded.

Two different phases can be drawn in the clinical course of COVID-19: a first phase (7-10 days) characterized by viral replication and cytopathic effect, and a second phase associated to hyperinflammation and high cytokine release (i.e., cytokine storm), and characterized by progressive lung involvement, and escalating needs of oxygen supplementation and/or ventilatory support (14). Fever preceded dry cough, dyspnea, and chest tightness by several days, but the intervals observed varied widely and tended to be longer among the series included in this review (3-21 days). It has been hypothesized that, on one hand the immunosuppression may provoque a delay in viral clearance, while on the other hand, this therapy may induce some protective effect to the occurrence of fatal critical pneumonia caused by the hyperimmune response (15). However, a more rapid clinical progression than the general population has been noted in COVID-19 KTRs (13). This fact is confirmed by the data extracted from the series regarding hospital and intensive care unit admissions (76-100% and 20-57%, respectively), and the comparative disproportion of patients managed in an outpatient basis (22-29%). A possible explanation for this fact may be a potential selection bias, since the vast majority of the patients sought care presumably for severe symptoms, were hospitalized and derived for ICU care accordingly, and were included within the 3-week period (range:6-45 days) of hospitalization follow-up conducted by most centers. This fact is in line with the observation provided by Pereira et al. (16), who affirm that hospitalized cohorts, particularly those presenting dyspnea, show higher rates of severe disease. Nonetheless, experience with other infections in kidney transplant recipients shows that potentially serious infections may have subtle or delayed presentations, that should be linked to more proactive approaches in the diagnostic evaluation and monitoring, and lower threshold for hospitalization (12).

Clinical classification of COVID-19 pneumonia includes mild, severe, and critical types (15). The cytokine storm, and hyperinflammation pattern due to antiviral immune response has been disscused as the driver for severe respiratory symptomatology and acute respiratory distress syndrome (ARDS). Many patients included in this review (42-84%) exhibited oxygen saturation levels ≤ 93% at some point during their admission, thus requiring respiratory support with oxygen supplementation (65-85%), non-invasive ventilation (10-41%), or mechanical ventilation (6-39%) depending on their particular situation and moment during the clinical course. The rates for mechanical ventilation observed among the series studied seems sensibly higher compared to that reported for the general population (39 vs. 15%) (1), but again a selection bias would explain this disproportion.

Similarly to what was observed in the SARS-CoV and MERS, the uptake of SARS-CoV-2 into the proximal tubular epithelium is a posible explanation for acute kidney injury (AKI) in COVID-19 patients. AKI has been reported in up to 15% and 29% of the overall, and critically ill COVID-19 patients in the general population (17). Variable degrees of proteinuria and hematuria have also been reported. However, the studies included in this review show a different reality regarding kidney transplant recipients. AKI has been observed in 21-60%, requiring aproximately 10% RRT. These findings may presumably be atributed to acute tubular necrosis. However, given the circumstances of demand for assistance, and risks associated to non-essential tests, no for-cause biopsy was performed in any center.

AKI would be present or subsequently developed in KTRs more frequently than in the general population. It has been observed that patients with triple manteinance inmmunosuppression schedules, and those that require immunossuppressive induction, or aggressive therapy with monoclonal/polyclonal antibodies for an ongoing acute rejection may experiment more se-

Table 2 - Summary of symptomatology, diagnostic test findings, and outcomes.

Author	Clinical presentation (symptom %)	Blood parameters (present/absent moderate <50% patients, intense>50% patients)	PCR test (%)	CXR (%)	SatO2 <93% (%)	Complic. Rate (%)	Outcome					Definitive outcome (%)
							Outpatient rate (%)	Hosp Adm (%)	ICU Adm (%)	Death rate (%)	Discharge rate (%)	
Banerjee D, et al. (14)	Fever (*) 71, Cough 42, Dyspnea 57, Myalgia 14	Lymphopenia, Intense elevation of CRP, D-dimer, LDH, ESR	100	100	57	ARDS 42 AKI 28 TE 14 Sepsis 14	29	71	57	14	14	57
Alberici, et al. (7)	Fever (*)100, Cough 50, Myalgia 5, Dyspnea 5	Moderate elevation of LDH, Urea and Cr Intense elevation of CRP, procalcitonin, ferritin, D-dimer	100	85	84	N/A	0	100	20	15	15	40
CUKTP (1)	Fever (*) 87, Cough 60, Myalgia 13 Diarhea 20	Lymphopenia, Moderate elevation of LDH, Intense elevation of CRP, ferritin, I-Troponin, ESR, IL-6	100	73	N/A	AKI 40	0	100	27	13	53	66
Zhang, et al. (24)	Fever (*)100, Cough (*)100, Myalgia 60	Lymphopenia, Moderate elevation of D-dimer and ESR, Intense elevation of CRP	100	100	N/A	N/A	0	100	0	0	40	40
Pereira, et al. (16)	Fever (*)70 Cough 59 Dyspnea 43 Myalgia 24, Diarrhea 31	Lymphopenia, hipoalbuminemia, Moderate elevation of Cr, I-Troponin, D-dimer, ferritin Intense elevation of CRP, procalcitonin, ferritin, and IL-6	100	100	42	N/A	24	76	34	24	54	78
Akalin, et al. (13)	Fever (*) 58 , Myalgia 22	Lymphopenia, thrombocytopenia, Moderate elevation of ferritin, CRP procalcitonin, and D-dimer	100	96	N/A	AKI 21	22	78	N/A	28	N/A	N/A
Zhu, et al. (15)	Fever (*) 90 Cough (*) 90 Dyspnea (*) 90 Myalgia (*) 90 Diarrhea (*) 90	Lymphopenia Moderate elevation of Cr, moderate elevation of liver enzymes	100	100	N/A	AKI 60 RRT 10	0	100	N/A	10	N/A	90
Montagut-Marrahi, et al. (18)	N/A	N/A	100	N/A	N/A	N/A	0	79	52	6	N/A	87
Nair, et al. (23)	Fever (*) 70, diarrea 20, coryza 10	Lymphopenia, Moderate elevation of CRP and ferrtin	100	N/A	N/A	AKI 50 RRT 10	0	90	50	30	70	100

PCR = polymerase chain reaction-test (positive result); **CXR** = chest-X-ray (findings); **$SatO_2$** = Oxygen saturation; **Adm** = admission; **ARDS** = acute respiratory distress síndrome; **AKI** = acute kidney injury; **LDH** = lactate dehydrogenase; **CRP** = C-reactive protein; **Cr**: serum creatinine; **ESR** = erythrocyte sedimentation rate; **IL-6** = interleukin-6; **RRT** = renal replacement therapy

(*) most frequent presenting symptom

vere COVID-19 symptoms, longer clinical course, and need for RRT. This observation would favor a transient reduction or cessation in some (or even all) the immunosuppressive agents used to avoid an infection worsening, and in turn a potentially increased risk for acute rejection.

In fact, acute rejection may play a role in some of the AKI cases observed, but an accurate diagnosis cannot be provided. Nevertheless, AKI and RRT seems to lead to worse prognosis and outcome, explaining in part the excess in mortality observed in the series included (up to 30%) in

comparison to that of the general population (0.2-21%, depending on age) for the general population and the KTRs, respectively (18). In fact, death seems more likely to be produced by extrapulmonary complications (i.e., thrombosis, sepsis) rather than from severe pneumonia or ARDS, reinforcing the idea that these complications, although scarce in frequency carry devastating consequencies in the short-term (3-week period until discharge or fatal event) (14).

COVID-19 diagnosis and follow-up protocol during admission

The initial diagnosis is currently based on at least one of the following: clinical suspicion, alterations in the blood sample analysis, and chest X-ray (CXR) findings. Suspicion should be confirmed by specific testing.

COVID-19 was uniformly confirmed (100%) by nucleic acid polymerase chain reaction (PCR)-testing of swab samples obtained from the nose and/or throat of the patients included. However, <10% false negative cases were detected. This fact is possible due to problems in the sampling techniques, variable viral load of the upper respiratory tract, and mutations of the virus gene. Repeated PCR-testing (whole genome viral sequencing) by experienced staff, along with blood SARS-CoV-2 antibody detection, may solve this problem and optimize diagnosis. In cases of limited access to tests, symptoms prevail. Any patient with history of recent exposure, or in the presence of suggesting symptoms must be always considered a candidate for testing, and managed as presumptively positive unless specified otherwise. In case of high suspicion and negative PCR-testing, a new test must be repeated after 48 hours, and the patient considered positive in the meanwhile (19).

Initial blood test has to include red and white cell blood counts, metabolic and liver function biochemical panels, coagulation parameters, erythocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (16). Serum levels of albumin, D-dimer, ferritin, Interleukine-6 (IL-6), and I-Troponin have been also reported of value in the initial diagnosis, and would serve to categorize the severity of the infection.

Lower lymphocite counts, elevated ESR and serum levels of CRP, procalcitonin, D-dimer, ferritin, IL-6, and I-troponin at any point of the clinical course were uniformly reported among the series studied (Table-2). The cause for lymphocite depletion remains unclear, although lymphocytes have been identified as a primary target of SARS-Cov-2 injury, and somehow may be considered a normal feature in those patients receiving immunosuppresion. However, a further drop in lymphocyte count beyond the baseline should suggest disease worsening, thus representing a prognostic factor for severe illness. Leukocyte and neutrophil counts may increase, suggesting a bacterial coinfection, pulse glucocorticoid administration, or acute rejection, and should be managed accordingly.

Elevated serum levels of D-dimer and I--Troponin were observed more frequently in those patients exhibiting more severe presentations, and should suggest the presence of microvascular thrombosis or disseminated intravascular coagulation, given the absence of clinically evident thromboembolic events (17). A lower serum albumin, and higher procalcitonin, CRP, and creatinine levels, should also be considered factors for worse prognosis (18, 9). Therefore, a recommendation is provided to test D-dimer, ferritin, procalcitonin, CRP, and I-Troponin levels in addition to routine biochemical determinations at the debut, and thereafter only in those patients not showing clinical improvement (20).

The vast majority of the hospitalized patients included in this study showed either uni- or bilateral patchy opacities or lobe condensations in the chest-X-ray (CXR), that may passed unnoticed in the first phase of the infection (10-30%), and became more evident later during the admission. Interestingly, an improvement in radiographic findings has been observed without specific antiviral treatment in 7-10 days after the beginning of the symptoms by Zhu et al. (15). Although they recommended seriated high-resolution chest computed tomographies to follow the course of the pneumonia, this strategy was strongly discouraged and not performed by most centers, as part of prevention efforts.

COVID-19 treatment and drug interactions with immunosuppression

Optimal COVID-19 management is still under debate, and the therapeutic approach still lacks significant evidence. Apart from symptomatic support therapy, nor specific treatment neither best practice guidelines still exist for the management for KTRs with COVID-19. However, enhancement of personal protection precautions, early identification, and timely management of affected patients seems to be crucial, particularly in this special subgroup.

The indication for antiviral therapy is uncertain, and there are no approved drugs in this regard to date. A biphasic pharmacological approach to treating SARS-CoV-2 has been proposed. During the first 7-10 days from the onset of symptoms (phase-I) antiretrovirals (oseltamivir, ritonavir, darunavir, lopinavir, cobicistat), remdesivir or *chloroquine/hydroxychloroquine* may be considered. After this initial period (phase-II) immunosuppressive (calcineurin inhibitors) and immunomodulatory drugs (tozilizumab, sarilumab) may be of benefit.

Chloroquine/hydroxychloroquine (400 mg/12h for 24 hours and 200/12 h for 10 days): evidence supports its antiviral activity against the SARS *in vitro*. However, clinical evidence to recommend its use remains limited, and is based on the outcomes of a small series showing negativization of PCR-testing after 3 days of treatment (21). Given the better tolerability and safer adverse event profile, hydroxychloroquine should be recommended. Azythromycin in combination with hydroxychloroquine has been associated to a higher probability of PCR-negativization and has been used variably (Table-3).

Second generation antiretrovirals lopinavir/ritonavir (200 mg/50 mg; 2 pills/12 hours; oral uptake for 14 days): Although a recent analysis failed to demonstrate significant benefit with lopinavir/ritonavir beyond the standard treatment for hospitalized adult patients with COVID-19, a higher proportion of patients experienced a clinical improvement, the interval to this improvement was shorter, and the patients were less likely to die from the disease or its complications (22). These data may support their consideration in the higher risk groups, including the KTRs. However, 71% of the patients included in one series showed improvement in lung infiltrates on imaging without any specific antiretroviral therapy after 7-10 days of admission (15).

Remdesivir (200 mg iv for 24 hours, and 100 mg iv/24 h for 9 days): this drug has shown proved efficacy in reducing the viral load and improving lung parameters in animal and *in vitro* models (incorporation to RNA chains) (19).

Corticosteroids (methylprednisolone 16 mg iv/24 h or equivalent prednisone): Given their anti-inflammatory effect, corticosteroids may be contraindicated in the phase-I of the disease, but conversely would have a role in phase-II, particularly in those patients exhibiting ARDS.

Tozilizumab (8mg/kg iv up to 800 mg) and *leronlimab:* these drugs would play a role in limiting the citokine release syndrome observed in phase-II, particularly in those exhibiting increasing requirements of oxygen or ventilatory support. A substantial decrease in the serum levels of IL-6, and parallel clinical improvement have been documented after 1-3 doses of treatment (13).

Ascorbic acid: The multicentric clinical trial CITRIS-AL suggests a mortality decrease with its use in those patients with ARDS. No other evidence supporting it is available (19).

Intravenous immunoglobulins (1 g/Kg/d for 2 days or 400 mg/Kg/d for 5 days): They have been used in cases of severe pneumonia in a case-by-case basis. Their use is still under debate (19).

All of the above mentioned agents are being used in the context of clinical trials or as off-label medications on the basis of *in vitro* outcomes or biologic plausibility. Such medications can be used as per institutional protocols, but attention must be paid to interactions with immunosuppressive medications in KTRs. Two interactions of primary importance are the prolongation of the QT interval, and alterations in the metabolism of tacrolimus. Tacrolimus may prolong the QT in-

Table 3 - Summary of COVID-19 specific treatment, immunosuppression schedule adjustment, and ventilatory support requirements.

Author	COVID-19 treatment			Immunossupression schedule adjustment							Ventilatory support		
	Antiviral (%, agent)	HC (%)	TZ (%)	IV GC (%)	ATB (%)	Anti-Mb (%)	CNI (%)	m-TOR I (%)	GC (%)	AB (%, cause)	O_2 Suppl (%)	Non-inv ventilat (%)	Mechanical Ventilat (%)
Banerjee D, et al. (14)	14 (oseltamivir)	0	0	0	14	M:14, H:85	M: 57, R:14 H: 14	--	--	--	85	28	28
Alberici, et al. (7)	0	95	30	100	55	H: 100	H: 100	H: 100	H: 100	H: 100	65	10	10
CUKTP (1)	0	100	6	0	60	H: 92	M: 85, R: 7 H: 7	--	M: 100	H: 13	N/A	N/A	27
Zhang, et al. (24)	100 (oseltamivir or albidol)	0	0	20	20	H: 80	R: 100	--	R: 80	I: 20 (acute rejection)	N/A	N/A	N/A
Pereira, et al. (16)	3 (remdesivir)	91	21	24	66	R or H: 88	R or H: 18	--	R or H: 7	I: 2 (induction/ acute rejection)	N/A	41	35
Akalin, et al. (13)	0	66	22 (16 leronlimab)	0	N/A	H: 86	H: 20	--	--	--	N/A	N/A	39
Zhu, et al. (15)	100 (umifenovir, oseltamivir, ribaviringanciclovir)	0	0	80	0	H: 90	R or H: 80	--	H:100	I: 70	100	30	0
Montagut-Marrahi, et al. (18)	100 (lopinavir / ritonavir, beta-INF, anakinra)	14	50	50	43	H: 100	--	H: 100	--	--	N/A	N/A	6
Nair, et al. (23)		100	0	30	100	H:100	H: 20, R:80	H: 100	H: 100	--	N/A	N/A	30

HC: hydroxychloroquine, **TZ**: tozilizumab; **IVGC**: intravenous glucocorticoids; **ATB**: broad spectrum antibiotics (including azythromicin); **Anti-Mb**: antimetabolite therapy; **CNI**: calcineurin inhibitors; **m-TOR I**: m-TOR inhibitors, **GC**: glucocorticoids; **AB**: monoclonal/polyclonal antibodies; **O2 Suppl**: oxygen supplementation; **Non-inv**: non-invasive; **Ventilat**: ventilation: **INF**: interferon; **R**: reduced; **H**:held; **M**: maintained; **I**: increased

terval itself in a dose-depending fashion, and its accumulation in the plasma may lead to fatal arrhythmia (torsades). Protease inhibitors (lopinavir/ritonavir) can dramatically increase tacrolimus serum levels by liver enzymatic inhibition. In addition, the combination of hydroxychloroquine and azythromicin may also increase the corrected QT--interval. Therefore, both drug combinations must be handled with extremely care when associated to tacrolimus. Conversely, no interactions have been described between tozilizumab and immunosuppresive drugs. Interestingly, no drug interactions have been reported among the series studied.

In addition, COVID-19 patients tend to be hypercoagulable, and prophylactic therapy with low molecular weight heparin or low-dose aspirin is strongly recommended. Apixaban has also be used for this purpose when D-dimer levels were higher than 3.0 microg/mL (19).

Outpatient management

KTRs with mild symptoms may be managed via telemedicine as outpatients, but this strategy should be used in a case-by-case basis given the risks for rapid decompensation and relative insensiveness in the assessment of dyspnea and vital signs, thus resulting unuseful in high-risk patients. In fact, a dramatic 25% of patients managed with this approach in the series by Akalin et al. died at home (13).

For an outpatient approach the following criteria have to be met: lack of fever, no dyspnea, and ability to maintain close communication with the transplant team. The patient should be

instructed for a 14-day period of self-isolation (or at least 7 days after resolution of the symptoms, whichever is longer). Fluid communication between patient and transplant team is crucial (every 48 hours) to assess not only for health, but for emotional status. Temperature should be checked twice daily and a close monitoring of progression or new development of symptoms is mandatory. A pulse-oximeter should be provided, to check oxygen saturation at least three times a day (12). An initial diagnosis is mandatory, and must include a blood sample test containing WBC count, lymphocyte count, CRP, basic metabolic panel, liver function test, and CXR. If the patient remains stable regarding symptoms, these tests should be repeated every 48-72 hours. The frequency of laboratory testing may return to baseline after clinical improvement. Conversely, if the laboratory tests worsen, then testing should be recommended in a shorter interval, and hospitalization should be strongly considered.

Criteria for hospitalization include one of the following: dyspnea, severe vomiting or diarrhea, inability to maintain oral hydration/medication uptake, confusion, persistent/worsening fever >38ºC, oxygen saturation <94%, significant laboratory abnormalities (AKI, acute liver injury), two consecutive abnormal readings (>70 mg/L) for high sensitivity-CRP, or abnormal CXR (12). Even when the patient does not meet the previous criteria, but is thought to be at high-risk of decompensation, unnable to provide adequate self-care, or a close communication with the transplant team is not possible, hospital admission should be encouraged.

Management of baseline immunosuppression regime

The management of immunosuppression in KTRs with COVID-19 is challenging, representing a delicate balance between infection control and allograft funtion. Maintaining or increasing the immunosuppressive load may impair viral clearance and facilitate infection progression, while holding or cessating it may precipitate an acute rejection. Firm evidence-based recommendations are not posible at this point due to a lack of sufficient experience, and therefore a wise case-by-case approach seems to be the most prudent management. Factors that would aid regarding this decision-making process include: age, comorbid conditions, severity of COVID-19 infection, time from transplantation, baseline graft function, prior history of rejection, and donor specific antibody panel (12, 13).

Decrease the doses of immunossuppressive drugs is based on the experience with other viral infections that may affect KTRs, and lower counts of CD3+, CD4+, CD8+ cells exhibited by these patients (13). Both situations may act in symbiosis to induce or worse a lymphocyte depletion. In addition, it has been suggested that patients receiving triple immunosuppression regimes present worse outcomes compared with those requiring manteinance with dual immunosuppression therapy alone when infected by COVID-19 (14, 23, 24). In the series conducted by the Columbia University Kidney Transplant Program, those patients requiring ICU admission, artificial ventilatory support, or those who died (15%) were receiving a triple immunossuppression regimen. This fact may reinforce the belief that an association must exist between the immunosuppresive load and predisposition to a more severe infection requiring hospitalization, ICU admission, or death (1). Interestingly, reducing immunossuppresive therapy for a short interval do not seem to lead to acute rejection in the short-term, in the light of the experience provided in this review. However, the long-term effect is still uncertain.

Therefore, mild symptomatic patients may be managed with the immunossuppression regimen unchanged. The manteinance of the immunosuppressive schedule may not compromise the antiviral immune effect in mild-to-moderate symptomatic patients either. In this way, the usual practice in patients with mild-to-moderate symptoms is to continue (preferable) or make reductions in the immunosuppresive drugs, according to worsening symptomatology. Definately, the no-modification approach may favor an increase in mortality rates for those patients requiring hospitalization, and thus an aggresive reduction of immunosuppression must be considered in cases of severe pneumonia or ARDS.

On the basis of experience with BK virus and CMV infections, a 50% dose reduction

or complete cessation of antimetabolite drugs is appropriate (12). However, if the patient is worsening according to the laboratory findings, antimetabolites should be completely discontinued.

The appropriate time for reduction and the potential role of calcineurin inhibitors (CNI) during the hyperinflammatory phase of the disease remains unknown. The recommendation is to maintain tacrolimus and adjust to 4-6 ng/mL, based on the experience in treating BK virus nephropathy. However, some authors recommend withholding in cases of severe pneumonia. An argument favoring the use of Cyclosporin-A mantainance is based on on its ability to limit the viral proliferation in diverse coronaviruses (through its impact on ciclophylin A and B) (25). However, switching from Tacrolimus to Cyclosporin-A does not seem recommended. On the other hand, the increased levels of cytokines (IL-6 and others) and hyperactivated status (CCR6+, and Th17) in CD4+ cells suggested for the phase-II, may be limited with the use of Tacrolimus (26, 27).

In regard to induction therapy, it is possible that lymphocyte-depleting antibodies would increase the risk for worsening, thus cessation in KTRs exhibiting severe symptoms seems prudent. However, a case-by-case decision based on the particular risk-benefit situation is encouraged. Betalacept administration should be deferred, and the patient should be converted to an alternative agent.

Finally, the optimal reintroduction of immunosuppressive agents after discharge remains unclear. Current estimates are that the viral shedding can occur for up to 14-37 days after symptomatic improvement. In addition, a probable association between the viral load, symptoms severity, and viral shedding has been suggested. Therefore, the number of variables makes difficult to adopt a standardized interval regarding the reintroduction of immunosuppression. Nevertheless, to differ reintroduction at least for 2 weeks after symptoms improvement is recommended, recognizing the increased risk for allograft rejection in the interim.

CONCLUSIONS

The sudden spreading of COVID-19 across the globe has brought uncertanty regarding the diagnosis and treatment of the disease. Although general understanding is improving, information about select patient subgroups, such as KTRs, remains limited and deserve special consideration. The ideal treatment for KTRs with SARS-CoV-2 infection remains unclear, and the answers regarding its optimal management still rely on expert opinion. Although many of the patients included in this review experienced a favorable outcome, the small cohort and varied therapy makes it difficult to draw any meaningful conclusion beyond that of short-term safety and tolerability of the currently available protocols. Long-term follow-up is required to better understand the prognosis and sequelae of COVID-19 in KTRs.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Exploring Urological Experience in the COVID-19 Outbreak: American Confederation of Urology (CAU) Survey

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ABSTRACT

Purpose: To explore the current situation faced by Latin American urology departments during the COVID-19 Outbreak in terms of knowledge, actions, prioritization of urology practices, and implementation of internal clinical management protocols for inpatients and outpatients.

Material and Methods: A non-validated, structured, self-administered, electronic survey with 35 closed multiple choice questions was conducted in Spanish, Portuguese, Italian, and English and Deutsch versions from April 1st to April 30th, 2020. The survey was distributed through social networks and the official American Confederation of Urology (CAU) website. It was anonymous, mainly addressed to Latin American urologists and urology residents. It included 35 questions exploring different aspects: 1) Personal Protective Equipment (PPE) and internal management protocols for healthcare providers; 2) Priority surgeries and urological urgencies and 3) Inpatient and outpatient care.

Results: Of 864 surveys received, 846 had at least 70% valid responses and were included in the statistical analyses. Surveys corresponded to South America in 62% of the cases, Central America and North America in 29.7%. 12.7% were residents. Regarding to PPE and internal management protocols, 88% confirmed the implementation of specific protocols and 45.4% have not received training to perform a safe clinical practice; only 2.3% reported being infected with COVID-19. 60.9% attended urgent surgeries. The following major uro-oncologic surgeries were reported as high priority: Radical Nephrectomy (RN) 58.4%, and Radical Cystectomy (RC) 57.3%. When we associate the capacity of hospitalization (urologic beds available) and percentage of high-priority surgery performed, we observed that centers with fewer urological beds (10-20)

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compared to centers with more urological beds (31-40) performed more frequently major urologic cancer surgeries: RN 54.5% vs 60.8% (p=0.0003), RC 53.1% vs 64.9% (p=0.005) respectively.
Conclusions: At the time of writing (May 13th 2020) our data represents a snapshot of COVID-19 outbreak in Latin American urological practices. Our findings have practical implications and should be contextualized considering many factors related to patients and urological care: The variability of health care scenarios, institutional capacity, heterogeneity and burden of urologic disease, impact of surgical indications and decision making when prioritizing and scheduling surgeries in times of COVID-19 pandemic.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging, highly infectious respiratory disease, that is caused by a novel coronavirus, now designated as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) that was first reported on 31st December 2019 in Wuhan, China and is considered responsible for a cluster of new cases of interstitial pneumonia (1). In response to this serious situation, the World Health Organization (WHO) declared it as a "Global Pandemic" on March 11th, 2020 and called for collaborative efforts of all countries to prevent the rapid spread of COVID-19 (2).

At the time of writing (13th May 2020) 4,262,799 cases were confirmed, 291,981 deaths reported with 187 countries around the world facing this health emergency (3). Many hospitals and urology departments have adapted resources, limited surgeries and delayed diagnostic procedures. Patients scheduled for major elective surgeries have undergone a triage to prioritize oncologic disease, given that delaying treatment may affect oncological patients´ survival and quality of life of oncologic patients. Internal management protocols and recommendations for inpatients and outpatients established by different international societies of urology, have been published to optimize patient care (4-6). Many questions regarding short and long-term effects of the pandemic araise: How should urologists act? Have we properly selected patients? Further concerns must be analyzed including different scenarios, health care systems, education, training and health situation with respect to the pandemic at this time.

Nevertheless, the battle against COVID-19 is still continuing worldwide. For Latin-America this threat represents a risk of collapse to all health care systems. The Latin American urological community, is represented by the American Confederation of Urology (CAU) which involves 24 urological societies in 22, conveys different scenarios in professional development and heterogeneous public health care infrastructures and policies influencing the way of facing the pandemic.

OBJECTIVES

To explore the current situation faced by Latin American urology departments during the COVID-19 emergency in terms of knowledge, actions, prioritization of practices, and implementation of internal clinical management protocols for inpatients and outpatients.

MATERIAL AND METHODS

This was an electronic survey based on a non-validated, structured, self-administrated questionnaire consisting of 35 closed multiple choice queries. It was conducted in Spanish, Portuguese, Italian and English versions. The survey was opened on April 1st and closed in April 30th 2020. The survey was distributed on-line through social networks, the official CAU website (7) and CAU mailing distribution list available at. <http://www.caunet.org/en/urology>, and anonymous mainly for from Latin American urologists and urology residents. The 35 queries explored different issues: 1) Personal Protective Equipment (PPE) availability and

design of internal managment protocols for healthcare staff; 2) Prioritization of surgeries and urological urgencies. The level of priority groups for procedures was categorizing into: a) High priority; b) Low Priority and c) No priority and 3) Inpatient and outpatient care activity.

Statistical Analysis

Categorical responses were expressed as its absolute values and percentages (%). In each issue analyzed we included if responses were categorized as excluded answers. Descriptive analyses were carried out. All variables were compared using chi-square test and multiple comparisons adjusted by Bonferroni´s method. In all cases a p value less than 0.05 was considered as statistically significant. Data analysis was performed using SPSS (Version 22, IBM Corp, New York, U.S.A.).

RESULTS

Of 864 surveys received, 846 had at least 70% valid responses and were included in the statistical analyses. Surveys corresponded to South America in 62% of the cases (distribution of 522 questionnaires: Argentina 116, Peru 75, Bolivia 70, Ecuador 64, Chile 48, Colombia 48, Venezuela 43, Uruguay 27, Paraguay 18 and Brazil 13), Central America and North America in 29.7% (distribution of 250 questionnaires: Mexico 97, Dominican Republic 34, Panama 26, Guatemala 23, Nicaragua 16, Costa Rica 11, El Salvador 11, Honduras 10, Puerto Rico 10, USA 9 and Cuba 3) and Europe and other countries the remaining 8.3% (distribution of 70 questionnaires: Spain 61, Italy 6, France 1, Portugal 1, Qatar 1, China 1).

Participants' age distribution was: less than 40 years in 36.3%, between 40 and 55 years in 39.5% and older than 55 years in 23.3%. In terms of gender 17% were female. Of 841 surveys which specifing educational level, 12.7% were residents in training; 362 (41.9%) trained urologists reported not having residents under their charge. In terms of urological clinical practice: 70% practiced general urology, 25% uro-oncology and 26% endourology. In terms of practice setting: 363 (43.2%) were in university hospitals and 249 (39.7%) in public and non-academic hospitals. Overall characteristics of the study population are shown in (Table-1).

PPE and internal management protocols

Regarding PPE and internal management protocols for healthcare provides, of 833 valid responses, 733 (88%) confirmed the implementation of specific protocols. Strikingly, only 455 (54.6%) professionals, received training on COVID-19 self-care protection protocols and 45.4% did not receive training to perform a safe clinical practice. Only 2.3% reported being infected with SARS-CoV-2; in contrast, the remaining 87.6% of non-infected urologists reported working in health care centers with proper internal management protocols. Lastly, 91.7% of urologists kept themselves updated about the latest news published publications regarding management protocols.

Priority of surgeries and urological urgencies

Analyzing surgical activity, 60.9% performed urgent procedures as ureter stentings (double J-stents, pigtail stents) or nephrostomy tube placement due to infection, obstructive lithiasis or both; in 50% of these cases, there was not any COVID-19 protocol available for urological urgencies; in 37.4% of the cases the patient was assumed to be COVID-19 positive without prior testing; and only 13% of patients received COVID-19 testing before hand.

Uro-oncologic surgeries were reported by 43.9% of participants, followed by endourologic procedures in 18.5% (mostly renal colic)(Table-2). Of 777 (100%) surveys completed, the following oncologic surgeries were registered as High-Priority: Orchiectomy 69.3%, Transurethral Resection of Bladder Tumor (TURB) 63.6%, RN 58.4%, RC 57.3% and Radical Prostatectomy 32.4%. In contrast, oncologic surgery was more commonly rendered as Low Priority in Partial Nephrectomy in 54.8% and no oncological surgeries, No Priority: Transurethral Resection of Prostate (TURP) in 48%. Regarding to surgical access: 73.8% of surgeries were performed by open approach and 26.2% by minimally-invasive surgery approach. Laparoscopic or Robotic, RN and Radical Prostatectomy were more frequently major

Table 1 - General Characteristics of study population.

Characteristics	Number (%)	Number (survey response type)
Country COVID-19 cases		**841 (exclusive)**
<500	239 (28.4)	
500-1000	119 (14.1)	
1001-5000	27 (32)	
> 5000	213 (25.3)	
Urologic Subspecialty		**838 (non-exclusive)**
General Urology	589 (70.3)	
Uro-oncology	210 (25.1)	
Andrology	50 (6)	
Endourology	221 (26.4)	
Functional Urology	72 (8.6)	
Pediatric Urology	68 (8.1)	
Practice Setting		**841 (non-exclusive)**
University Hospital	363(43.2)	
Private Center	461 (55)	
Public Hospital, non-university	249 (39.7)	
Military Hospital	49 (12.8)	
Others	20 (2.4)	
Urologic Beds		**810 (exclusive)**
10-20	582 (71.9)	
21-30	130 (16)	
31-40	98 (12.1)	
More than 40	0	
Urologic COVID19+Beds		**777 (exclusive)**
No cases	646 (83.1)	
1-5 cases	68 (8.8)	
6-20 cases	51 (6.6)	
More than 21 cases	12 (1.5)	

uro-oncologic surgeries. In 43.2% scheduling and prioritizing surgeries as well as decision making was performed by the urologist in charge. 57.7% decided to postpone the surgery when the use of blood derivates was being planned and 42.3% were performed under standard protocol (Table-3). In terms of potential use of Intensive care unit (ICUs) for high-priority surgeries, 75.6% decided to postpone procedures and 13.8% performed them under a COVID-19 internal management protocol. When we associate the capacity of hospitalization (urologic beds available) vs % of the high priority surgeries performed, we observed that centers with fewer urological beds (10-20) vs. those with more urological beds (31-40), the later performed more major urologic cancer surgeries, such as RN (54.5% vs. 60.8; p=0.0003), RC (53.1 vs. 64.9; p=0.005), compared to those with more urological beds (31-40),respectively. Other oncological surgeries such as: Orchiectomy (68.2% vs. 67.7%;

Table 2 - Urological activity during COVID-19 period.

Issue	Number (%)	Number (survey response type)
Types of scheduled surgeries		**816 (non-exclusive)**
Only urgencies	497 (60.9)	
Uro-oncology	358 (43.9)	
Andrology	12 (1.5)	
Endourology	151 (18.5)	
Functional Urology	33 (4)	
Pediatric Urology	15 (1.8)	
External consultation management		**820 (non-exclusive)**
Closed	405(49.4)	
Telephone calls	264 (32.2)	
Teleconsultation (Video Calls: Skype, Facetime, Zoom)	131 (16)	
No changes	63(7.7)	
Only follow up visits	187 (22.8)	
Procedure to follow in urgencies surgeries		**812 (exclusive)**
No specific protocol	402 (49.5)	
Patient is assumed to be COVID-19 Positive Protocol	304 (37.4)	
Test COVID-19 to evaluate patient status	106 (13.1)	
Surgical treatment decision maker		**777 (non-exclusive)**
Local Uro-oncologic Committee	194 (24.9)	
Responsible Urologist	336 (43.2)	
Service Chief	269 (34.6)	
Uro-oncology Unit Chief	68 (8.8)	

p=0.078), TURB (61.7% vs. 62.5%; p=0.110), Penectomy (56.1% vs. 51.1%; p=0.223) and Radical Prostatectomy (30.1% vs. 33.3%; p=0.121) did not show statistically significant differences. On the other hand, 16.9% of urological beds were assigned to COVID-19 positive patients without urological conditions (Table-4).

Inpatient and outpatient care activity

In terms of urologic cancer care, 76.2% reported that their centers continued to provide oncological treatments, including intravesical instillations or chemotherapy, and 25.4% of internal radio-oncology departments continued with a regular treatment schedulea.

Regarding to urologic outpatient´s follow--up, many hospitals or healthcare systems have reported the implementating technologic resources into the provision of urologic consultations in order to supply recommendations and prescriptions. Of these, 32.2% used telephone calls and 16% adopted telemedicine thus connecting to platforms as facetime, skype and zoom.

DISCUSSION

The World Health Organization declared COVID-19 as a “Global pandemic” and public health emergency on March 11th, 2020, calling for collaborative efforts from all countries to prevent

Table 3 - Priority of urologic surgeries during COVID-19 pandemic in Latin American urologic departments.

Surgery	No priority (%)	Low priority (%)	High priority (%)	Surveys included
Radical prostatectomy	120 (15.8)	394 (51.8)	246 (32.4)	760
Partial nephrectomy	116 (15.6)	408 (54.8)	220 (29.6)	744
Radical nephrectomy	66 (8.6)	252 (33)	446 (58.4)	764
Radical cystectomy	90 (12.1)	228 (30.6)	428 (57.3)	746
TURB	59 (7.7)	221 (28.7)	490 (63.6)	770
Retroperitoneal Lymphadenectomy	118 (16.1)	386 (52.7)	228 (31.1)	732
Orchiectomy	59 (7.7)	177 (23)	534 (69.3)	770
Penectomy	76 (10.1)	251 (33.4)	425 (56.5)	752
BPH	363 (48)	352 (46.6)	41 (5.4)	756
Lithiasis	139 (18.1)	402 (52.2)	229 (29.7)	770

Table 4 - Association between Capacity of Hospitalization (urologic beds available) vs High Priority Surgeries Performed in COVID-19 pandemic.

	Urologic Beds Number			
Surgery	10-20	21-30	31-40	*p* value
Radical Prostatectomy	157 (30.1)	50 (40)	32 (33.3)	0.121
Partial Nephrectomy	146 (28.6)	39 (31.4)	29 (30.9)	0.286
Radical Nephrectomy	285 (54.5)	93 (74.4)	59 (60.8)	**0.0003**
Radical Cistectomy	270 (53.1)	88 (70.4)	61 (64.9)	**0.005**
TURB	324 (61.7)	91 (71.7)	60 (62.5)	0.110
Retroperitoneal Lymphadenectomy	144 (29)	44 (35.8)	29 (30.9)	0.505
Orchiectomy	362 (68.2)	97 (77)	63 (67.7)	0.078
Penectomy	290 (56.1)	77 (62.6)	47 (51.1)	0.223
BPH surgery	28 (5.4)	8 (6.5)	3 (3.2)	0.556
Lithiasis treatment	157 (29.7)	37 (28.9)	26 (27.1)	0.975

the rapid spread of the disease (2). At this time (May 13th, 2020) 4,262,799 cases have been confirmed, 291,981 deaths have been reported with 187 countries around the world are facing this health emergency, which representing a risk of collapse for all health care systems (3).

Many hospitals and healthcare urologic centers around the world have adapted resources, limited surgeries as well as diagnostic procedures and have postponed major elective surgeries. Internal management protocols and recommendations for inpatient and outpatient care, have been provided by different international societies of urology to optimize patients´ management , including decreasing the general inflow of patients to hospitals and reducing the number of medical and surgical procedures, therefore ensuring that only urgent and non-deferrable oncological surgeries are performed (4-6).

On February 28th, the president of the Robert-Koch-Institute (RKI) in Berlin, Germany suggested to defer all non-urgent surgeries (8).

Similarly, in most of European National Health Systems a reduction of surgical activity was recommended. Several definitions of deferrable and non-deferrable procedures have been proposed by panels of experts from all around the world, taking into account several factors, including the aggressiveness/severity of each disease, the impact of short term delays to care and the availability of alternative treatment modalities (4-6).

Our study provides data from 22 Latin American countries that may contextualize the ongoing recommendations on selection of high-priority major uro-oncologic surgeries as RN 58.4% and RC 57.3% which are more frequently performed in Latin American urologic centers with less capacity of hospitalization (10-20 urologic beds available) compared tocenters with more capacity (31-40 urologic beds available). Our findings have practical implications and should be analysed considering many factors related to patients and urologic care: the variability of health care scenarios, the volume capacity at each center, the volume and variability of urologic disease, the impact of surgical indications and decision making when prioritizing and scheduling surgeries in times of the COVID-19 pandemic. Oderda et al. (9) conducted a survey involving 57 European urological referral centers. They showed that the management of the main urological cancers has been altered dramatically by the COVID-19 pandemic, with most European centers (82%) declaring to be "much" or "very much" affected. Uro-oncological consultations for newly diagnosed cancers and follow-up were more than halved or almost suspended, in 55% and 71% of centers, respectively.

At present, the constant requirement of beds and mechanical ventilators in ICUs has increased due to the influx of critical patients requiring ventilatory support, transforming surgical areas into intensive care spaces, thus decreasing the capacity of surgical areas; making clear that prioritizing urological urgencies is essential. Stensland et al. (10) defined a list of urological conditions and surgical procedures that patients may undergo during the pandemic, stressing a more conservative approach whenever feasible. For example, benign prostate hyperplasia (BPH) and urinary tract stones should be treated only if complications occurs, with catheterization, and nephrostomy or ureteral stenting respectively. Surgery should be maintained just for urological urgencies, such as testicular torsion, refractory gross hematuria or oncologic disease.

Our data reported that 60.9% performed urgent procedurs such as ureteralstenting or nephrostomy placement due to infection, lithiasis or combination of both.

At this time, an adequate use of PPEs for healthcare providers and specific internal management protocols are essential to contain the spread of the virus (11). In this study, 88% of the participants confirmed the implementation of specific protocols in their urologic centers, but only 2.3%, reported being infected with COVID-19. Probably this low percentage of contagion may be due to the period (April 1st - April 30th 2020) in which the survey was conducted; at that time in Latin American countries the number of COVID-19 positive cases reported was lower than in Europe. It is important to emphasize that the number of healthcare providers infected reported around the world is correlated to adequate use and availability of PPE as well as the number of tests performed to confirm the presence of SARS-CoV-2.

During this exceptional situation, most hospitals and healthcare providers in critically affected areas are changing their on-site activity to telehealth medicine in order to reduce hospital visits to the minimum necessary (12, 13). In this context, telemedicine, particularly video consultations have been promoted for reduce the risk of transmission and to facilitate the follow-up in urologic consultations, medical recommendations, prescriptions and the surgical follow-up of discharged. In our data 16% of urologists have implemented the use of telemedicine in order to continue with clinic activity at home.

This survey has several limitations: the participation from some countries was limited, many urologist may not have taken part in the survey due to the number of other surveys exploring the impact of COVIID-19 in urologic practice. To properly interpret our results it is fundamental to consider the variability of health care scenarios across Latin American countries, the hospitalization capacity at each center (beds, mechanical

ventilators, ICUs, equipment), the volume and variability of urologic disease, the health situation of each Latin American country with respect to the pandemic at the time of the survey analysis, the impact of surgical indications and decision making when prioritizing as well as scheduling surgeries in times of COVID-19 pandemic.

CONCLUSIONS

At the time of writing, our data represents a snapshot of COVID-19 outbreak in the Latin American urological practice. Our findings have practical implications and should be contextualized considering many factors related to patients and urological care: the variability of health care scenarios, the volume capacity at each center, the volume and variability of urological disease, the impact of surgical indications and decision making when prioritizing as well as scheduling surgeries in times of COVID-19 pandemic.

The COVID-19 era represents one of the biggest challenges is modern health care history. Urological practice has been severely impaired beyond the tragic effects of this emergency. However, several opportunities for improving urological research, clinical and surgical care of outpatient and inpatient settings have been rapidly developed, creating an excellent feedback of knowledge among the urological community around the world.

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CONFLICT OF INTEREST

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ORIGINAL ARTICLE

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Impact of COVID-19 Pandemic on Ibero-American Urology Residents: Perspective of American Confederation of Urology (CAU)

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ABSTRACT

Introduction: Since World Health Organization (WHO) declared COVID-19 as a global pandemic, urology services have developed strategies to prioritize and not to differ urgent and oncological patient's medical attention, in order to optimize resources and decrease infection probability among staff and patients. This unprecedented situation has generated a decrease in assistance and academic activities in most medical residences. The aim of this manuscript is to evaluate the impact of this health crisis on training programs through a survey addressed to urology medical residents.

Materials and Methods: Cross sectional designed study, with multiple-choice non validated survey answered online by residents. Questionnaire was developed through the CAU EDUCACION platform.

Results: A total of 148 responses from 18 countries coming from Latin America and Spain answering the survey. Of total, 82% answered that the activity of their urology department was significantly reduced, attending only urgent surgical pathologies, 15 % that, the urology activity has been closed completely and the staff was assigned to COVID-19 patients care, 3% continue with the regular clinic activity. Likewise, 75% stated that their surgical training has been completely affected, 93% receive urological information through tools such as Skype, ZOOM meeting, Cisco Webex, being Webinar modality the most used. Despite technological boom, 65% answered their academic training has been partially or completely affected. Most of the surveyed residents consider that period of residence should be extended to retrieve the educational targets.

Conclusion: This unprecedented reality is negatively impacting the heterogeneous residency programs that American Confederation of Urology (CAU) nucleates. It is necessary to continue with technological innovation and allocate time and resources to easily generate accessible tools to favor the training of future urologists.

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INTRODUCTION

Since World Health Organization (WHO) declared COVID-19 (SARS-Cov-2 Coronavirus) as a global pandemic on March 11, 2020, affected countries health systems have determined measures increasingly restrictive in order to contain population and decrease virus spread. In northern hemisphere countries, where contagion curve suffered an abrupt growth, urology departments started limiting their activity according to health system saturation.

Latin American countries had adopted preventive measures, postponing any activity that did not imply an emergency in surgical field to avoid health personnel and available beds occupation (1).

This behavior purpose is to increase sanitary capacity, increase anesthesiologists availability for acute respiratory crisis management, and avoid contagion among patients with elective urological pathologies. However, urology services developed new protocols to prioritize urgent patients with oncological pathologies care that cannot be deferred (2).

This unprecedented situation is significantly affecting the already heterogeneous residency programs in Urology American Confederation (Confederación Americana de Urología, CAU) area in terms of duration, continuous evaluation systems, accreditations and re-certifications, as well as with regard to training and access possibility to new surgical technologies and urological diagnosis (3).

Our objective is to evaluate the impact of the COVID-19 pandemic on academic and surgical training activity of residents in urology across Ibero-American countries that comprise CAU.

MATERIALS AND METHODS

Cross sectional designed study, in which multiple-choice non validated survey with 10 closed questions in Spanish version was carried out, which were answered anonymously online by residents of different academic training years, using their mobile devices or personal computer.

Questionnaire was developed through the CAU EDUCACION platform and was distributed by social media and email in the period from April 23rd to April 29th, 2020. A simple descriptive analysis was carried out.

RESULTS

A total of 148 (100%) responses were obtained from medical residents of Argentina, Brazil, Bolivia, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Spain, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Dominican Republic, Peru, Uruguay and Venezuela. (Figure-1 shows the percentage of response by country).

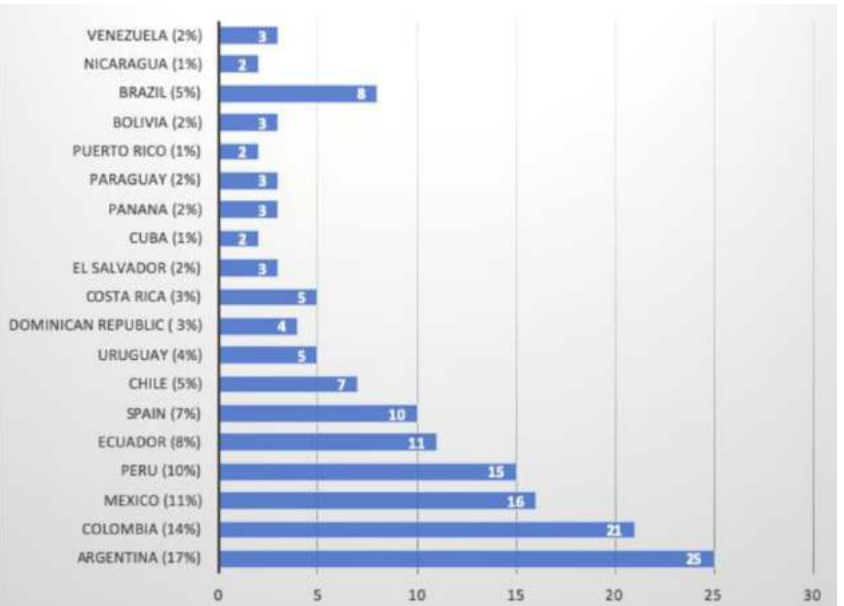
A total of 24 (16.2%), were residents studying the first residence training year, 33 (22.3%) second, 34 (23%) third, 35 (23.6%) fourth and 22 (14.9%) fifth year.

Regarding urology services where residents carry out their activities current functioning, 121 residents (82%) reported that activity was significantly reduced, solving only urgent surgical pathologies such as testicular torsions, obstructive lithiasis, priapism, urological trauma, urosepsis or oncological diseases that could not be postponed according to main urological societies recommendation guidelines.

On the other hand, 23 (15%) responded their service has completely closed activity to dedicate itself to patients with suspected COVID-19 respiratory pathologies care. Only 4 respondents (3%) reported regular activity, attending to non-urgent pathologies patients, carrying out functional pathologies diagnostic studies and elective surgeries to correct urinary incontinence, benign prostatic hyperplasia, non-oncological penile scrotal pathology and lithiasis surgeries which do not require immediate resolution.

Of total, 134 residents (90%) have presented changes regarding their clinical activity. Workweeks are alternate, since they take turns with their colleagues to carry out basic administrative service work, they carry out patient´s follow-up by telephone or telemedicine and they also collaborate with associate doctors in urological emergency surgery.

Figure 1 - Report of percentages of responses by Country.



Only 9 (6%) are working exclusively in first line of care for patients with COVID-19 suspected respiratory pathology, while 5 (4%) are carrying out their usual tasks.

Main concern of residents surveyed is negative impact that this health crisis is generating on their surgical learning curve. Thus, 37 (25%) residents reported their activity in operating room has been partially interfered, while 111 (75%) stated their surgical training has been completely affected.

Regarding current academic resident´s status, 138 (93%) acquire urological information through massive online dissemination tools with platforms such as Skype, ZOOM meeting, Cisco Webex, with Webinar (videoconference) modality being the most widely used, followed by pre-video edited surgeries, Journals clubs and Podcasts. Remaining 7% (10) do not carry out any online training type. But despite technological rise of these applications, 96 (65%) respondents affirm their theoretical training has been partially or completely affected, while the remaining 52 (35%) report that they have not undergone any change in their academic activity.

Due to this situation, 117 (80%) residents consider, based on their respective training programs, that measures should be taken being the most suggested to extend the residence period.

DISCUSSION

In this COVID-19 outbreak scenario, a worrying residency program situation is evident, which aims to be a challenge both for trainers and for doctors in training, considering also uncertainty generated by not knowing this pandemic duration.

In addition to decrease in care and urology services training activities, clinical recommendations are that few non-deferrable surgical procedures that are performed be carried out by experienced doctors to reduce surgical times, risks of infection and complications (4, 5).

Urological field has undergone gradual modifications according to alert level escalation in each country by COVID-19. In general, inter-hospital training instances were suspended, admissions exams to residencies were delayed, and face-to-face academic activities were suspended, beginning a new stage in scientific dissemination where applications such as ZOOM meeting, Skype and Webex Cisco play a critical role to interaction between residents and experienced physicians (6, 7).

This unexpected period has provided an opportunity to explore different virtual learning options and should increase tools implementation such as telemedicine, smart training programs, and surgical skill development activities monitored by expert urologists (7, 8).

From the CAU residents and young urologists office, scientific outreach programs have been successfully carried out through uro-oncological topics presentations through AULA VIRTUAL platform (9), as well as Ibero-American residents participation is encouraged through the contest ¨Camino a Guayaquil 2020¨, which started in November 2019, and encourages all doctors continuous training within urological societies that comprise CAU, and it also promotes important scholarships obtainment.

Periodic virtual athenaeums development, clinical cases discussion, bibliographic reviews and surgical techniques through videos and simulation would provide a fundamental and complementary contribution (10).

Although these modalities do not replace learning process in operating rooms, they represent a challenge and encourage new educational technology strategies generation that could be incorporated in educational programs in the future.

Limitations of this study were the short disclosure time and the low number of responses with respect to the total number of urology residents in each country, and the strengths were the number of countries that participated that allowed giving a representative outlook on Spain and Latin America residents reality.

CONCLUSIONS

This unprecedented reality has a negative impact on the heterogeneous residency programs at the American Confederation of Urology.

Main residents concern is focused on their surgical training.

Online modalities such as Webinar and Podcast are the most widely used and are currently a fundamental tool for continuous updating.

Most respondents suggest measures such as extending residency program to retrieve the educational targets.

We encourage entities responsible for training residents to continue with technological innovation and to allocate time and resources to generate easily accessible tools, such as surgical simulators, step-by-step videos of surgeries, and tutored surgical skills development programs tutored by experienced physicians to reduce the impact of this situation on learning curves and favor future urologists training.

ABBREVIATIONS

CAU = American Urology Confederation
COVID-19 = Coronavirus disease 2019
SARS-Cov-2 Coronavirus = Severe acute respiratory syndrome coronavirus 2

CONFLICT OF INTEREST

None declared.

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Implementation and strategies to ensure adequate coordination within a Urology Department during the COVID-19 pandemic

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ABSTRACT

Purpose: to provide an update on the management of a Urology Department during the COVID-19 outbreak, suggesting strategies to optimize assistance to the patients, to implement telemedicine and triage protocols, to define pathways for hospital access, to reduce risk of contagious inside the hospital and to determine the role of residents during the pandemic.

Materials and Methods: In May the 6th 2020 we performed a review of the literature through online search engines (PubMed, Web of Science and Science Direct). We looked at recommendations provided by the EAU and ERUS regarding the management of urological patients during the COVID-19 pandemic. The main aspects of interest were: the definition of deferrable and non-deferrable procedures, Personal Protective Equipment (PPE) and hospital protocols for health care providers, triage, hospitalization and surgery, post-operative care training and residents' activity. A narrative summary of guidelines and current literature for each point of interest was performed.

Conclusion: In the actual Covid-19 scenario, while the number of positive patients globally keep on rising, it is fundamental to embrace a new way to deliver healthcare and to overcome challenges of physical distancing and self-isolation. The use of appropriate PPE, definite pathways to access the hospital, the implementation of telemedicine protocols can represent effective strategies to carry on delivering healthcare.

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INTRODUCTION

A novel coronavirus was identified and considered responsible for a cluster of new cases of interstitial pneumonia in December 2019, in Wuhan, China. On February 11th, 2020, the disease caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus 2) was officially termed "COVID-19" by the World Health Organization (WHO) (1). The high potential of human to human transmission led to a rapid COVID-19 epidemic in China, and subsequently, the

WHO declared COVID-19 as a global pandemic on March 11th (1). In Europe, Italy has been one of the most affected countries and the first one to adopt important restrictive measures on the whole national territory (2).

At the time of writing (May 7th, 2020), 3,833,547 total cases were reported. Of these, there were 2,261,992 symptomatic patients. Those in intensive care unit (ICU) represented 2%. Overall, 265,210 deaths have been reported in Italy. Meanwhile, the spread of the disease has dramatically increased in the USA, making it the leading country for total cases and total deaths (3).

All countries affected by COVID-19 are facing the major problem of ICU overcrowding and the progressive lack of resources. Many hospitals have to postpone major elective surgeries. Hospital departments worldwide limit procedures to urgent and non-deferrable cases, following the adoption of internal inpatients and outpatients management protocols. With the exponential increase in the number of cases, all countries had to reallocate medical resources to manage COVID-19 patients, with redistribution of medical and surgical activities (4).

To provide a snapshot of the current uro-oncological management in Europe during the COVID-19 emergency, Oderda et al. conducted a survey involving 57 European urological referral centers. They showed that the management of the main urological cancers has been altered dramatically by the COVID-19 pandemic, with most European centers (82%) declaring to be "much" or "very much" affected. Uro-oncological consultations for newly diagnosed cancers and follow-up were more than halved or almost suspended, in 55% and 71% of centers, respectively (5). Guidelines have been provided by major national and international scientific societies to aid physicians in the management of urological conditions during the COVID-19 outbreak.

We aim to summarize the current state of literature on the management of a Urology Department during the COVID-19 outbreak, suggesting strategies to optimize assistance to the patients, to implement telemedicine and triage protocols, to define pathways for hospital access, to reduce risk of contagious inside the hospital and to determine the role of residents during the pandemic.

MATERIALS AND METHODS

On May 8th, 2020 we performed a review of the literature through online search engines (PubMed, Web of Science and Science Direct). We looked at recommendations on management of urological patients during the COVID-19 pandemic provided by the European Association of Urology (EAU) and the EAU Robotic Urology Section (ERUS). The main aspects of interest were: the definition of deferrable and non-deferrable procedures, Personal Protective Equipment (PPE) and hospital protocols for healthcare providers, triage, hospitalization and surgery, post-operative care, training and residents' activity.

A narrative summary of guidelines and current literature for each point of interest was performed.

Deferrable and non-deferrable procedures

ICUs are being filled up rapidly, causing a shortage of hospital beds, mechanical ventilators and anesthesiologists. To decrease the general inflow of patients to hospitals, recommendations have been provided to reduce the number of medical and surgical procedures ensuring that only urgent and non-deferrable oncological surgeries are performed. On February 28th, the president of the Robert-Koch-Institute (RKI) suggested to defer all non-urgent surgeries (6). Similarly, in most of European National Health Systems a reduction of surgical activity was recommended. Several definitions of deferrable and non-deferrable procedures have been proposed. In particular, the EAU guidelines categorized procedures into priority groups (Table-1):

1) emergency, life-threatening situations that cannot be postponed for more than 24 hours; 2) high priority, the last to postpone because of the concrete possibility of a clinical harm;
3) intermediate, should be cancelled but recommended not to postpone for more than 3 months. Clinical harm (progression, metastasis, loss of organ function) is possible if postponed 3-4 months but unlikely and;
4) low priority, that can be postponed for more than 6 months (7).

Table 1 - Summary of EAU guidelines Office Rapid Reaction Group for oncological and non-oncological conditions (7).

	PRIORITY	CONDITION	TREATMENT
Oncological	**Emergency**	Life threatening– organ function threatening condition	Cannot be postponed more than 24 hours.
	High priority	Clinical harm (progression, metastasis, loss of organ function and deaths) if postponed > 6 weeks	The last to cancel, prevent delay of > 6 weeks.
	Intermediate priority	Clinical harm possible (progression, metastasis, loss of organ function) if postponed 3 months but unlikely	Not recommended to postpone more than 3 months Reconsider in case of increase in capacity
	Low Priority	Clinical harm very unlikely (progression, metastasis, loss of function) if postponed	Postpone up to 6 months

	PRIORITY	CONDITION	TREATMENT
Non-oncological	**Emergency**	Life threatening situation	Cannot be postponed more than 24 hours.
	High priority	Clinical harm very likely if postponed > 6 weeks	The last to cancel, prevent delay of > 6 weeks.
	Intermediate priority	Clinical harm possible if postponed 3-4 months	Not recommended to postpone more than 4 months
	Low Priority	Clinical harm very unlikely if postponed	Postpone 6 months

Stensland et al. (8) defined a list of urological conditions and surgical procedures that patients may undergo during the pandemic, stressing a more conservative approach whenever feasible. For example, benign prostate hyperplasia (BPH) and urinary tract stones should be treated only if complication occurs, with catheterization, and nephrostomy or ureteral stenting, respectively. Surgery should be maintained just for urological urgencies, such as testicular torsion, refractory gross hematuria and oncological disease (i.e. invasive muscle bladder cancer, suspected high grade T1 bladder cancer, kidney tumors >cT3) (Table-2). The Research Urology Network (RUN) group has outlined priorities for urological patients (Table-3), providing strategies for the management of urological patients not suspected of, or positive for COVID-19 (4). Treatments that ensure a fast discharge with the resolution of functional harms should be used. For instance, in

Table 2 - Summary of suggested triage of urological surgical cases during the COVID-19 pandemic by Stensland et al. (8).

	CONDITION	PATHOLOGY	TREATMENT RECOMMENDED	COMMENTS
Stensland et al.	**Bladder cancer**	MIBC (regardless CHT) – refractory CIS (3rd line)	Radical cystectomy	5-8 days hospital stay
		Suspected ≥cT1 BC	TURB	Outpatient procedure
	Testicular cancer	Suspected testicular cancer	Orchiectomy	Outpatient procedure
		Post-CHT LN (testicular cancer)	RPLN dissection – RT/CHT post-orchiectomy (if clinically appropriate)	Balance CHT (immunosuppression)
	Renal tumor	≥cT3 renal tumor	Radical nephrectomy + thrombectomy	
		cT1 renal tumor	Delay surgery / Ablative approach	
		cT2 renal tumor	Delay surgery up to 3 months	
	Prostate cancer	PCa high-risk	RT – Surgery (if ineligible for RT) – delay in selected cases	Most prostatectomy should be delayed
		PCa intermediate/low risk	Delay surgery	
	Upper urinary tract cancer	High grade ≥cT1 UTUC	Nephroureterectomy	1 – 4 days of hospital stay
	Adrenal tumor	Adrenal tumor >6 cm (suspected for carcinoma)	Adrenalectomy	0 – 1 day of hospital stay
		Adrenal tumor <6 cm	Consider to delay	Possible rapid progression
	Urethral/penile tumor	Urethral/penile invasive or obstructive cancer	Limited data, consider partial penile penectomy, avoid LN dissection	Outpatient procedure
	Endourology	Stones	Nephrostomy/stent (preferable under local anaesthesia)	Emergency if obstructive/infected
		Indwelling ureteral stent	Delay most procedures (from 6-12 to 30 months)	Outpatient procedure
		BPH	Only if obstructive suprapubic/urethral catheter	
	Female urology/incontinence	Urinary incontinence	Delay all procedures	
		Cystitis	Delay all procedures	
		OAB	Delay all procedures	
		Neurogenic Bladder	Delay all procedures	
		External nerve stimulator	Internalized or removed	High risk of infection
	Reconstructive surgery	Fistula with pelvic sepsis	Urine/fecal diversion (delay definitive repair)	
		Infected urinary sphincter	Explantation	
	Urethral stricture	Urethral obstruction	Suprapubic/urethral catheter	Outpatient procedure
	Prosthetic surgery	Penile prosthesis	Explant if infected	
	General urology	Priapism	Shunt	
		Spermatic cord torsion	Detorsion/orchidopexy	
		Refractary gross hematuria	Clot evacuation	
		Acute scrotal abscess and Fournier's gangrene	Surgery	
		Penile/testicular fracture	Surgery	Outpatient procedure
		Ureteral injury	Surgery	
		Bladder perforation	Surgery	
	Transplant	Renal transplant	Deceased donor, don't delay Live donor, delay	
	Infertility	Infertilty	Delay all procedures	

MIBC = muscle-invasive bladder cancer; BC = bladder cancer; CHT: = chemotherapy; TURB = trans-urethral resection of bladder; LN = lymphnodes: RPLN = retroperitoneal lymphnodes; RT= radiation therapy; PCa = prostate cancer; BPH = benign prostate hyperplasya; OAB = overactive bladder;

Table 3 - Summary of RUN group recommendations for urological conditions during Sars-CoV-2 era (4).

RUN Group	**Urgent**	Upper urinary tract obstruction/infection	Nephrostomy/stent (preferable under local anaesthesia)
		Acute urinary retention	Urethral/suprapubic catheter
		Clot retention	Cystoscopic clot evacuation - TURB/TURP
		Spermatic cord torsion	Manual derotation/surgery
		Infection of artificial sphincter/prothesis	Explant
		Scrotal abscess	Drainage
		Fournier's gangrene	Surgery
		Priapism	Corpora cavernosa aspiration/irrigation or Shunt (preferable under local anaesthesia)
	Non-deferrable	MIBC / refractory CIS	Radical cystectomy + Urinary diversion (high virus load in stool)
		NMIBC(>2cm/high grade)	TURB + intravesical therapy
		Testicular cancer	Radical orchiectomy
		Post-CHT retroperitoneal residual LN	Surgery
		cT3-T4 renal tumor	Radical nephrectomy ± thrombectomy
		cT2	Radical/partial nephrectomy
		High grade >cT1 upper urinary tract urothelial cancer	Nephrouretectomy + LN dissection
		High-risk/locally advance PCa unsuitable for RT or ADT	Radical prostatectomy + LN dissection
		>cT1G3 penile cancer	Partial penectomy ± groin LN dissection
	Semi-non-deferrable	PCa intermediate/high-risk	Radical prostatectomy
		NMIBC (<2cm/low grade)	TURB
		cT1b renal tumor	Radical nephrectomy
	Deferrable	cT1a renal tumor	Partial nephrectomy
		Uncomplicated urinary stones	Medical therapy
		BPH with LUTS	Medical therapy
		Urinary incontinence	Medical therapy
		Genitourinary prolapse	Medical therapy
		Male urethral disease	Medical therapy
		Prosthetic surgery	Medical therapy
		Infertility	Medical therapy
		Suspected PCa	Postpone prostate biopsy
		NMIBC follow-up	Postpone flexible cystoscopy
		Ureteral stent or Nephrostomy tube	Postpone replacement up to 6 months
		Low-grade NMIBC	Postpone intravesical therapy
	Replaceable with other treatments	High-risk/locally advanced PCa	RT or ADT (if cannot receive timely curative treatments)
		Small renal tumor	Ablative treatment not requiring general anaesthesia
		Testicular cancer + retroperitoneal LN	RT or CHT

TURB = trans-urethral resection of bladder; TURP: trans-urethral resection of prostate; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive bladder cancer; CHT = chemotherapy; PCa = prostate cancer; BPH = benign prostate hyperplasya; LUTS = lower urinary tract symptoms; RT = radiation therapy; ADT = andogen deprivation therapy; LN = lymphnodes.

Table 4 - Summary of COVID-19 task force actions regarding PPE for HWs (13).

Front Office staff working		Healthcare personnel in contact with patients					Laboratory staff in contact with biological samples
At station in direct contact with patients	*At station with protective glass*	*In contact with a suspected or confirmed case of COVID-19*	*In contact with a patient who presents symptoms of fever and / or cold and / or cough*	*Performing endoscopic procedures*	*Assigned to take a biological sample for COVID-19 + patient*	*Anesthesiologists performing intubation*	
frequent hand hygiene by using 60 % alcohol solution	frequent hand hygiene by using 60 % alcohol solution	FFP2 filtering mask (use FFP3 only for the procedures that generate aerosols)	FFP2 filtering mask (use FFP3 only for the procedures that generate aerosols)	FFP3 filtering masks	FFP3 filtering mask	FFP3 filtering mask	FFP3 filtering mask
wear the FFP2 filtering mask during the entire work shift	/	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes	goggles or visors to protect eyes from biological liquids 'splashes
wear protective glasses from liquids splashes during the entire work shift	/	water repellent PPE coat	/	water repellent PPE coat	water repellent PPE coat	water repellent PPE coat	water repellent PPE coat
provide a surgical mask, supplied at the desk, to be worn by the patient with visible respiratory symptoms	provide a surgical mask, supplied at the desk, to be worn by the patient with visible respiratory symptoms	double gloves	gloves	gloves	double gloves	double gloves	double gloves

cases of upper urinary tract obstruction, ureteral stents or percutaneous nephrostomy are preferred to more definitive procedures such as PCNL (Percutaneous nephrolithotomy) or RIRS (Retrograde intra-renal surgery). In cases of gross hematuria, surgery should be limited to cystoscopy for clot evacuation and concomitant hemostasis, preferably in an outpatient setting. However, bladder tumors should be removed if identified. The aim of these conservative approaches is to limit the need for blood transfusions and post-operative intensive care bed occupation. Considering the limited resources, urgent and emergent urological conditions are suggested to be treated under local or regional anesthesia whenever feasible to reduce aerosol generation (4).

The RUN group divided uro-oncological procedures into four categories: non-deferrable; semi-non-deferrable; deferrable; and replaceable with other treatments. Non-deferrable surgeries include muscle-invasive or high-risk progression bladder cancer, testicular cancer, renal tumor >T2, upper urinary tract cancer ≥cT1, high-risk prostate cancer unsuitable for radiation therapy (RT), and penile cancer >cT1G3 (4). For these pathologies, a delay could result in poorer cancer-related outcomes. If a hospital struggles with limited resources due to an uncontrolled COVID-19 spread, the patient should be transferred to a lower impact area for treatment. High-complexity surgery carries higher rates of morbidity and mortality and, in cases where patient's health is not jeopardized, it should be delayed (9). For selected patients not fit for major surgery, conservative approaches such as bladder-sparing treatments, may provide comparable oncological outcomes without affecting patients' comorbidities and safety (10). However, it has to be considered that the delay of surgical treatment of non-emergent oncological cases could lead to poorer standard oncological outcomes, affecting survival (11). In COVID-19 positive patients, non-emergent procedures should be postponed, while urgent surgeries have to be performed in a separated and dedicated operating theatre, following local institution recommendations for protection of the operating staff (11). Finally, all interventions for benign uncomplicated disease should be deferred until the end of the pandemic (4).

PPE and hospital protocols for healthcare providers

The main goals for urologists and all health-care providers during the COVID-19 pandemic are to prevent patients from getting COVID-19, protect themselves as health care professionals, and deliver optimal urological care. To reach these goals, all medical personnel should comply with the PPE regulations. PPE includes: gloves, medical masks, goggles/face shield, gowns and aprons. For specific procedures, respirators (i.e. N95 or FFP2 standard or equivalent) are recommended (12). An adequate use of PPEs is essential to limit and contain the spread of the virus (Table-4) (13). Effective preventive measures for the community, according to the WHO, include: performing hand hygiene frequently with a 60% alcohol-based solution avoiding touching eyes, nose, and mouth; practicing respiratory hygiene by coughing or sneezing on to the bent elbow or tissue; wearing a surgical mask and performing hand hygiene after its disposal; maintaining the social safe distance (a minimum of 1 meter) (12). To keep the risk of infection as low as possible, it is important to monitor temperature with thermoscan before each work shift, use PPE correctly and perform periodic swab for all health care providers (14).

Triage

Hospitals should be divided into COVID-19 free and COVID-19 hospitals. The aim of triage is to stop any possible COVID-19 positive patient to access a COVID-19 free hospital. Accordingly, triage should be organized in hierarchic parts. Firstly, a telephone interview is required to enquire about clinical history, such as the presence of flu symptoms, sore throat, cough, fever, cold, intestinal symptoms and dyspnea within 3 weeks, and also about epidemiological history, such as a direct contact with a positive COVID-19 patient or origin from a red zone area. If there are no suggestions of a possible COVID-19 infection, the patient can be accepted to the hospital for the second phase of triage. At this stage, the patient is asked to wear a surgical mask, protective gloves and to follow all the recommended hygiene rules. The patient will then undergo thermoscan for the evaluation of the body temperature and all pre-hospitalization tests will be performed including chest x-ray and pharyngeal swab for COVID-19. Since most of the elective procedures are performed for malignant pathology it will be important, as far as staging is concerned, to strictly follow the guidelines thus avoiding non-essential tests, a valid aid to maintain the safety distance between patients. Simonato et al. proposed reducing the number of beds per room and/or to ensure the minimum safety distance between beds (15).

Hospitalization and surgery

Hospital transmission was reported to be responsible for 41% of the nosocomial SARS infection (16). To prevent the spread of COVID-19 among healthcare providers, all staff members should be monitored with periodic swabs and, when serology tests become available, should undergo serology testing. For inpatients, social safe distance should be granted with all beds at least one meter away from each other. Since there is no vaccine nor cure for SARS-CoV-2, the spread of the virus should be stopped by preventing close contact (17). The spread from dry surfaces contaminated with secretions of infected people has been proven in previous studies (18). For this reason, an accurate cleaning of surfaces, following local hospital recommendations, has to be done systematically.

Elective surgeries have been cancelled to prevent any potential risk of infection of the patient and surgical team. Research protocols and experimental treatments have to be avoided and surgeries must be performed by skilled surgeons according to the standard approach in order to reduce operative time, post-operative complications and to spare resources. Any kind of surgery may increase the transmission risk of respiratory tract infections that could induce life-threatening outcomes, in case COVID-19 diagnosis is missed (19). For this reason, during intubation and extubating, the surgical team should wait outside the operating room, and all intubation maneuvers should be performed in negative-pressure operating theatre wearing appropriate PPE (20). Operative rooms usually have positive pressure technology in their aseptic zone (operating area) and are separated only by doors. These sliding barriers imply that

the laminar air flow will be disrupted once doors are opened letting particles and aerosols to circulate freely. That is why it has been recommended to set up operating rooms at negative pressure to reduce COVID-19 dissemination beyond the theatre. The more people in the operating room, the more air-turbulences could worsen, regardless of the positive or negative pressure system (21). Therefore, there is the need to reduce the surgical team number to the minimum. Urologists were, and are pioneers of minimally invasive surgery (MIS): from endoscopy to robot-assisted laparoscopic surgery. MIS has been shown to reduce post-operative complications and peri-operative blood transfusions when compared to the open approach (22), supporting the need to limit the use of blood derivatives due to the decrease in blood donation. In order to spare resources, MIS should be performed where possible, by experienced surgeons outside of their learning curve (4).

Until now, there is little evidence on the differences in the risk of virus spread between MIS and open surgery (23). The possibility of theatre staff contamination during open, laparoscopic or robotic surgery is of a concern in case of a positive patient. Measures to reduce aerosolization in the operating room, such as insufflators continuous cycle, closed circuits fume extraction and performing surgeries at the lowest intraabdominal pressure allowed, should always be considered. Avoiding the use of two-way pneumoperitoneum insufflators is suggested to prevent the colonization of circulating aerosol in the insufflator or pneumoperitoneum circuit (24). Even if previous research has shown that laparoscopy promotes the aerosolization of viral pathogens present in the blood (25-27), currently, there are no specific data proving an aerosol spread of the SARS-CoV-2 during minimally invasive abdominal surgery (24).

It is known that any form of electrosurgery can produce smoke, with a potential of aerosolization. Li et al. showed that only 10 minutes using ultrasonic or electrical equipment during laparoscopy was sufficient to have a significantly higher particle concentration of the smoke compared to open surgery (28). Gas has a low mobility in the pneumoperitoneum, and this leads to an accumulation of aerosol formed during procedure in the abdominal cavity. A sudden release of trocar valves, larger skin incisions or incorrect trocar removal before the complete disinflation can expose the theatre staff to potentially infected pneumoperitoneum aerosol (23). Thus, operating room staff must confirm the complete and correct disinflation of the pneumoperitoneum at the end of every procedure. Otherwise, the proven benefits of MISs in terms of reduced post-operative complications and length of stay, as well as the advantages of ultrafiltration of most or all aerosol particles, must be strongly considered. Filtration of aerosolized particles can be more difficult during open surgery (26, 27).

Post-operative care

During the post-operative phase, the hospital stay should be reduced to the minimum without compromising patients' health. The aim is to discharge patients early, avoiding the onset of post-operative complications or even hospital readmission. In an ideal COVID-19 free hospital, patients should have undergone at least one nasopharyngeal swab with negative result before returning home. With regards to triage, post-operative care should be performed remotely whenever possible: lower infection rates among the staff and reducing patients contact are the main purposes to pursue (29). Laboratory values and pathological reports could easily be sent by e-mail, followed by a phone consultation and discussion. Cremades et al. found no difference in clinical results, and a similar number of patients required extra visits after the initial follow-up (30). Analogue results have also been shown in other previous studies (31, 32).

Training

The COVID-19 outbreak has led to cancelation or minimization of all elective major deferrable surgeries (33). In Italy and Spain, patients with scheduled oncological interventions were moved to hospitals considered COVID-19 free (13, 33). Even face to face and diagnostic activities underwent a great reduction, and in some cases a complete cancellation. The COVID-19 pandemic will have a profound effect

on surgical education for the foreseeable future. The Centers for Disease Control and prevention recently recommended avoiding any gatherings with more than 10 people (34). As a result, face to face academic activities, including teaching conferences and simulation labs should be avoided. The rotations between different institutions and abroad fellowships have been limited or cancelled, as rotating through different hospitals may significantly increase the risk of contagion for residents, patients, and other healthcare personnel. In addition, national and international urological conferences, such as the EAU and the American Urology Association (AUA) congresses have been postponed, cancelled or converted to a telematic format (35). The EAU guidelines, the American College of Surgeons (ACS), and even many government institutions, are suggesting to cancel elective surgery (7, 36) and most facilities are minimizing participants in any operation to essential personnel only. A recent survey conducted by Amparore et al. showed an overall decrease in daily residents' exposure. Overall, 41.1% experienced a reduction of on call duties, 81.2% of ambulatory visits, 74.1% of diagnostic procedures, 62.1% of endoscopic surgery, 57.8% of open surgery and 44.2% of MIS. This decrease was even more pronounced for last year trainees (37).

In some countries, such us Italy, France and UK redeployment of urology residents has occurred allocating them to work on medical wards or ICU. Furthermore, the debate on the participation of trainees in clinical activity during the COVID-19 outbreak is still open. In some countries, tutors and educators suggest residents to stay home and step down if they are not required for any clinical or ward duties (38). Many residency programs have responded to the pandemic by assembling rotating teams to cover their urology services, reducing the risk of COVID-19 exposure to patients and residents alike (39). These factors will undoubtedly decrease resident case volume and will impact strongly on every aspects of their training. However, it is of note that health crisis could lead to an opportunity for trainees to improve skills not acquirable during the normal practice: how to manage urology patients during a pandemic.

In this scenario to avoid a complete slowdown of the residents' training and a possible burnout, that is already relatively high compared to other specialties (39), it is important to introduce new and alternative teaching methods such as smart learning. Webinars, podcasts, prerecorded sessions, social media and platforms, such as the EAU education section (https://uroweb.org/education/online-education) and the EAU Surgery in Motion School (https://surgeryinmotion-school.org/) are all important tools to reduce the effects of the SARS-CoV-2 pandemic on residents training and to continue with the theoretical learning.

CONCLUSIONS

In the current COVID-19 pandemic, while the number of positive patients globally are rising, it is fundamental to embrace a new way to deliver healthcare and to overcome challenges of physical distancing and self-isolation. In this review, we provided an insight into the COVID-19 overall situation and presented a picture of the current state of art in terms of the impact on urological patients, surgeons and trainees, providing practical recommendations.

Telemedicine is playing a crucial role because it can be used to support patients during an infectious pandemic to minimize contacts and the risk of SARS-CoV-2 exposure, reducing unnecessary hospital access, empowering patient's self-care, and also maintaining resident training. Even if the containment of the pandemic burst is currently the main purpose of all countries health and economic systems, we can't lose the focus on maintaining the best standard of care for non-urgent pathologies. A problem that we will soon have to cope with is the accumulation of cases delayed during this pandemic and the consequent extent of surgical waiting lists. A precise subdivision of hospitals into COVID-19 positive and COVID-19 free, and strictly following hygiene precautions will allow urological surgical activity to carry on, reducing the number of postponed cases.

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CONFLICT OF INTEREST

None declared.

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The Covid-19 pandemic seen from the frontline

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ABSTRACT

COVID-19 disease caused by infection with the SARS-CoV-2 virus produces respiratory symptoms, predominantly of the upper airways, which can progress to pneumonia after 7 days with persistent fever, cough and dyspnea, and even develop a syndrome of acute respiratory distress (ARDS), multi-organ failure and death. Since COVID-19 disease was declared by the WHO there has been a redistribution of the healthcare system for these types of patients, especially in the front line, which is, in primary care, emergencies and in intensive care units (ICU). In primary care, the fundamental role is the diagnosis of the suspected patients, follow-up mainly by telemedicine (specially telephone calls) to detect warning signs in case of worsening and subsequent referral to the emergency department; as well as explaining home isolation measures. In the emergency department, it is included the management of suspicious cases and, if it any risk factor is found, complementary tests are carried out for precise diagnosis and admission assessment; In case of oxygen saturation <95% and poor general condition, valuation is requested for admission to the ICU. Depending on the severity of the patient, he/she would be or not a candidate for invasive mechanical ventilation, which must be performed by trained personnel to prevent the spread of the infection minimizing the risk of contagion. ARDS's treatment strategies include pulmonary protection ventilation, prone position, recruitment maneuvers and, less frequently, oxygenation by extracorporeal membrane. Among the specific treatments for COVID-19 stand out mainly drugs to reduce viral load, although sometimes specific drugs will be needed to treat hyperinflammation, hypercoagulability and concomitant infections.
One of the goals to be achieved is for patients to recover and be able to successfully return to work; for this purpose, an adequate physical and psychological rehabilitation program is essential, as about 50% have symptoms of anxiety and depression.

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INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is currently a pandemic declared by the WHO on March 11, 2020, therefore, a public health emergency (1). As the pandemic has intensified, health systems have established protection standards and technical follow-up documents for the management of patients in different areas, including primary care, hospital emergencies, in the front line of medical care and transfer to the intensive care unit (ICU) of patients with serious complications; with

emphasis on measures to protect patients and health personnel against the virus. In many cases, the desire for widespread masking is a thoughtful reaction to pandemic anxiety (2). Based on recent information, we provide a summary regarding to the diagnosis, management and treatment of the COVID-19 patient from the first line: Primary health care emergency and intensive care unit.

The following is a brief summary of the virus causing the disease(1, 3, 4):

1.1. It is a zoonotic virus, SARS-CoV-2 with the first case in Spain in late January 2020.
1.2. Binds to angiotensin-converting enzyme 2 receptors in alveoli.
1.3. Sensitive to heat and disinfectants.
1.4. Transmission by respiratory drops and contaminated fomites.
1.5. No demonstrated airborne or feces transmission.
1.6. On plastic surfaces it lasts 72 hours, stainless steel 48 hours, cardboard 24 hours, copper 4 hours, in air after aerosols 2 hours.
1.7. Prodromal phase 1-2 days before symptoms start, up to 14 days if moderate or severe.
1.8. Transmission of 1.5 - 4 cases by an infected.
1.9. COVID-19, the serial interval is estimated at 4·4–7·5 days, which is more similar to severe acute respiratory syndrome (SARS).
1.10. Estimates suggest that about 80% of people with COVID-19 have mild or asymptomatic disease, 14% have severe disease and 6% are critically ill.

EVIDENCE ACQUISITION

For carrying out the systematic search of the literature, we used online databases such as PubMed, Cochrane, Google Scholar, UpToDate; Among the search criteria referring to COVID-19, we highlight RCTs published in the last 3 months, in humans, in English and Chinese languages; In the search criteria regarding supportive treatment as pharmacological, the search was extended to the last 15 years. The most frequently used descriptors were “coronavirus infections”, “Primary Health Care”, “Emergency Medical Services”, “Intensive care unit”, “pneumonia”, “Respiratory Distress Syndrome Adult”. As well as the publications of the Technical Documents of the Ministry of Health of the Government of Spain on the diagnosis, management and treatment of COVID-19.

1 - CLINICAL MANIFESTATIONS

The WHO mission report in China describes the most common symptoms and signs of laboratory-confirmed cases, including fever (87.9%), dry cough (67.7%), asthenia (38.1%), expectoration (33.4%), dyspnea (18.6%) (5).

In Spain the most common symptoms reported are fever, cough, dyspnea and chills; 40% developed a digestive clinic (diarrhea or vomiting). Men have a higher prevalence of fever and dyspnea, while sore throat and digestive clinic are significantly more common in women.

It is characterized by(5):

1.1. COVID-19 syndrome: Coronavirus disease 2019 (COVID-19) is a potentially serious acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The set of clinical manifestations caused by SARS -CoV-2 infection includes from mild respiratory symptoms to severe pneumonia with respiratory distress syndrome, septic shock and / or multi-organ failure. The development of these complications largely depends on the patient’s prior immune status.
1.2. They are classified into:
1.2.1. Asymptomatic Infection: state in which there are no symptoms and the transmissibility of SARS--CoV-2 can occur in this condition up to a minimum of 2 days before the onset of symptoms.
1.2.2. Mild cases: Characterized by an upper respiratory infection (fever, dry cough, odynophagia, nasal congestion, headache, myalgia). Symptoms are gene-

rally present for about two weeks until recovery (20 days).

1.2.3. Moderate cases: characterized by respiratory symptoms and pneumonia, pulmonary infiltrates that progress in 24 to 48 hours, these patients may or may not be admitted.

1.2.4. Severe cases: those that require hospitalization, who present dyspnea, tachypnea, O2 Saturation <93%; of which approximately a third require admission to the ICU (Adult Respiratory Distress Syndrome, Sepsis, Shock). Most of these complications appear 7 days after the onset of symptoms and recovery in 3 to 6 weeks.

2 - DIAGNOSIS

2.1. The microbiological diagnosis of COVID -19 is carried out using the Polymerase Chain Reaction (PCR) technique, determining the Ribonucleic Acid (RNA) of the SARS-CoV-2 virus, therefore, it is the diagnostic test per excellence.

2.2. Rapid antigen or antibody detection techniques are not considered adequate for diagnosing acute infection. ELISA-type serology or other high-performance immunoassay techniques are not indicated by themselves for diagnosis in the acute phase of the disease (6). There is the total antibody test indicated in symptomatic patients with several days of evolution and the test that differentiates immunoglobulin M (IgM) and immunoglobulin G (IgG) indicated in both symptomatic and asymptomatic patients to know their immunological situation (healthcare professionals, nursing homes, contacts).

2.3. The sample studied is blood obtained from venous blood or a lancet digital puncture (4).

2.4. These diagnostic tests will be carried out on symptomatic patients in the hospital setting with moderate or severe involvement, whether or not they have negative PCR: If the result is positive, the diagnosis is confirmed (recent or past infection) and if the result is negative, PCR will be performed (2).

2.5. In the non-hospital setting, mild symptomatic cases will be made with priority to nursing homes.

2.6. In the community setting, it may be possible to carry out a rapid diagnostic test in patients with high clinical suspicion and several days of symptom evolution.

2.7. Rapid tests in healthcare professionals: It will be carried out on those professionals with clinical suspicion of COVID -19 with negative PCR and more than 7 days after the onset of symptoms in order to confirm the diagnosis (Table-1).

2.8. Professionals without COVID-19 symptoms: Rapid test must be carried out with the purpose of early detection of asymptomatic cases that might be transmitters of SARS- CoV-2 (Table-2).

3 - DETECTION AND MONITORING OF THE PATIENT WITH SARS-CoV-2 IN PRIMARY CARE

3.1 - Identify suspected cases, diagnose, treat and isolate them (mild cases), explaining the isolation measures at home (ventilated site and preferably use of a single bathroom) (7) and provide continuous care giving confidence and security to the patient. No proof of detection of SARS -CoV-2 in these patients. 80% of patients infected will be mild and will not require admission.

3.2 - In the monitoring of mild cases, the appearance of warning signs, especially from 7 - 8 days of evolution such as worsening cough, shortness of breath and fever more than 7 days; and if any appears, patients should be trans-

Table 1 - Usage of rapid tests in symptomatic professionals. April 2020.

Outcome	Interpretation	Action Guideline
IgM + IgG +	COVID-19 confirmed	Repeat PCR
IgM + IgG -		
IgM - IgG +	Contact with COVID-19	Assess repeat PCR based on symptoms
IgM - IgG -	Discharged for COVID-19 (if after more than 14 days).	If the 14 days have not passed and there is suspicion clinical, repeat PCR and rapid test.

Table 2 - Rapid tests in asymptomatic professionals. April 2020.

Outcome	Interpretation	Action Guideline
IgM - IgG -	Discharged for COVID-19	
IgM - IgG +		
IgM + IgG -	COVID-19 cannot be ruled out	PCR will be performed
IgM + IgG +		

ferred to the hospital for evaluation.

3.3. In primary care, treatment is symptomatic; do not give empirical antibiotics unless there is a clinical suspicion of overinfection. In those cases azithromycin or levofloxacin is recommended.

3.4. Regarding the removal of isolation in minor cases, it is carried out at 7 days without clinical symptoms and/or 20 days since the opening of the follow-up episode.

3.5. Confirmed patients who have required hospital admission and who have been discharged with positive PCR must maintain home isolation and monitor their clinical situation for at least 14 days from hospital discharge and perform confirmatory negative PCR; If it turns out positive, isolation is carried out for 14 more days and at least 7 more days for a new PCR (7).

3.6. The population is informed of the importance of avoiding to go out from their home, just for essential activities, hygiene measures and social distancing.

4 - MANAGEMENT OF THE PATIENT WITH SARS-CoV-2 IN EMERGENCIES:

4.1. **General population:**

4.1.1. In cases with mild symptoms (do not require hospital admission) home isolation and care follow-up were indicated previously (8).

4.1.2. General guidelines for the evaluation of patients with infection acute respiratory in the Emergency department (Table-3).

4.1.3. In all patients with respiratory infection when is necessary hospital admission, PCR for COVID-19 will be requested, and must remain in isolation (Table-4).

4.1.4. Emergency Treatment: Therapeutic measures will be used according to the clinical severity of the patient (Table-5).

4.1.5 - In summary, it is concluded that all suspicious patients (fever, cough, dyspnea) who go to the emergency room, ventilatory mask and isolation, anamnesis

Table 3 - Ministry of Health, Consumption and Social Welfare (MSCBS). General measures for evaluation in the emergency department of the general population. April 2020 (8).

Patient <60 years, without fever or respiratory insufficiency (O2 saturation and respiratory rate in normal ranges for age, ≥ 96% and <20 breaths per minute respectively) or co-morbidity	• Usual evaluation. • Registration according to usual criteria. • Chest radiography according to the criteria of the clinician. • Do not request the PCR for COVID-19 in patients who are going to be discharged.
Patient <60 years, with fever and without respiratory failure (saturation ≥ 96% and respiratory rate <20 breaths per minute respectively) or comorbidity: X-ray will be performed in function of the clinician's judgment	• If the patient does not have pneumonia, regular evaluation and discharge according to usual clinical criteria. PCR should not be requested to COVID-19 in patients who are to be discharged. • If the patient has pneumonia (regardless of the characteristics of the radiological infiltrate), perform analysis (blood count, coagulation, with D-Dimer and basic biochemistry with protein C reactive, Lactate dehydrogenase [LDH] and transaminases).
Patient > 60 years or with comorbidity	• X-ray and analytical (basal arterial blood gas, blood count, D-dimer coagulation, and basic biochemistry with C reactive protein, LDH and transaminases).

Table 4 - MSCBS. Discharge criteria in patients with Pneumonia due to COVID-19. April 2020 (8).

Pneumonia may be discharged in patients <60 years, with Pneumonia Severity Index (PSI) I-II, without radiological complications or analytical complications, if they do not present immunosuppression or significant comorbidity (including hypertension and diabetes).	Unilobar alveolar pneumonia. • Without dyspnea • With O_2 saturation and respiratory rate • normal • Lymphocyte number > 1200 • Normal transaminases • Normal LDH • D-dimer <1.000

Table 5 - MSCBS. Emergency treatment in patients with COVID-19. April 2020 (8).

Bronchodilators	• Use of pressurized cartridge associated with a spacer chamber (inhalers dried). • If there is a need for an aerosol, it must be in a room with negative pressure.
Oxygen therapy	• In respiratory failure or shock, oxygen with a filter mask exhaled until a saturation appropriate to the age and state of the patient.
Corticosteroids	• Do not administer systemically.
Fluid therapy	• Conservative management in severe acute respiratory failure without shock.
Septic shock	• Administer antibiotics early.

and vital signs (O2 saturation> 95%) should be the standard of care; if the patient is > 60 years old and do not present any risk factors (> 65 years, high blood pressure [HBP], Diabetes Mellitus [DM], Obesity, Heart disease, Disease Pulmonary, Renal, Liver, Immunosuppression) he/she is discharged with follow-up for primary care and home treatment. If the patient have any clinical alteration, chest Rx is requested, if it is normal but with O2 saturation <95%, PCR is performed with blood analysis, Legionella antigen and Pneumococcus antigen in urine, to the awaiting result will be in the emergency room. In cases where the chest Rx is altered the patient is entered or discharged according to clinical symptoms, if not presents risk factors or Fine (Pneumonia Severity Index [PSI]) I-II it is suggested to individualize (Figure-1).

In cases that present a Fine III or risk patient, request ICU assessment.

4.1.6. Regarding thromboprophylaxis, patients with COVID-19 without pneumonia receive home treatment (Table-6) (9).

4.2 - **Children:**

The COVID-19 symptoms in children are generally mild characterized by predominantly respiratory symptoms with cough, fever, and / or nasal congestion, as well as gastrointestinal symptoms. They have the same probability of contagion as adults, are a susceptible population and with high difficulty in controlling respiratory infections (disability for personal hygiene measures in minors) and ease for contagion. As well as the presence of asymptomatic infections or very slight that go unnoticed. Pediatric cases are, to date, scarce (10).

4.3. Pregnant:

4.3.1. Pregnant women are not more susceptible than the general population for the spread of the disease, nor for the development of complications in women without comorbidities (11).

4.3.2. Complications increase in patients with Human Immunodeficiency Virus (HIV), HBP, infection, lung diseases, receiving corticosteroid treatment or immunosuppressants. There is few scientific evidence for COVID-19 effects during the first and second trimester of pregnancy.

Table 6 - Spanish Society of Thrombosis and Hemostasis (SETH). Thromboprophylaxis in patients with COVID-19 who do not require admission. April 2020 (9).

Indication	Medical history of Venous Thromboembolic Disease. Thrombophilias. Cancer. Recent surgery. Pregnancy / puerperium. Hormone Therapy (withdraw anovulatory contraceptives).
Dose	Adjust according to weight and glomerular filtration rate. Enoxaparin: <80 kg 40 mg / dL > 80 kg 60 mg / dL. Bemiparin: 50 IU / Kg.
Duration	1-2 weeks. Encourage ambulation within the home.

4.3.3. There is no clear evidence of intrauterine transmission, and there is a risk of developing premature deliveries, loss of fetal well-being, and delayed intrauterine growth although they are infrequent.

4.3.4. The presence of SARS -CoV-2 in breast milk has not been demonstrated (11).

4.4. patient over 60 years old:

4.4.1. The factors that make this age group at high risk are the comorbidities (HBP, DM, chronic lung diseases, cancer or immunosuppression from another cause), higher concentration of angiotensin converting enzyme 2 (ACE2) receptors, living in a nursing home, along with the changes that take place in the immune system due to aging (12).

4.4.2. Nursing homes are the most vulnerable places therefore the isolation of the elderly and the control measures are essential in preventing the spread of COVID-19; and therein lies the importance of performing rapid antibody detection tests, since the cornerstone is to perform early identification and it is not necessary to wait for the presence of suggestive clinic.

5 - TREATMENT OF SARS-COV-2 PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT

In the different studies published, there is discrepancy in the series regarding the number of patients treated in ICU: from 7.7% (13) to 19.1% (14).

A comprehensive patient assessment is essential to evaluate the possibility of admission in the ICU. Once is decided, the patient will be moved to an isolated cubicle with closed suction system. In addition, it is essential to know the procedures that release aerosols, since extreme cautions must be exercised to avoid contagion. Some of these procedures are described below: nebulization, non-invasive ventilation, manual ventilation with mask and self-inflatable bag, tracheal intubation or tracheostomy, aspiration of secretions, bronchoscopy, cardiopulmonary resuscitation, supine--to-prone position change, daily personal hygiene and cleaning of bowel movements.

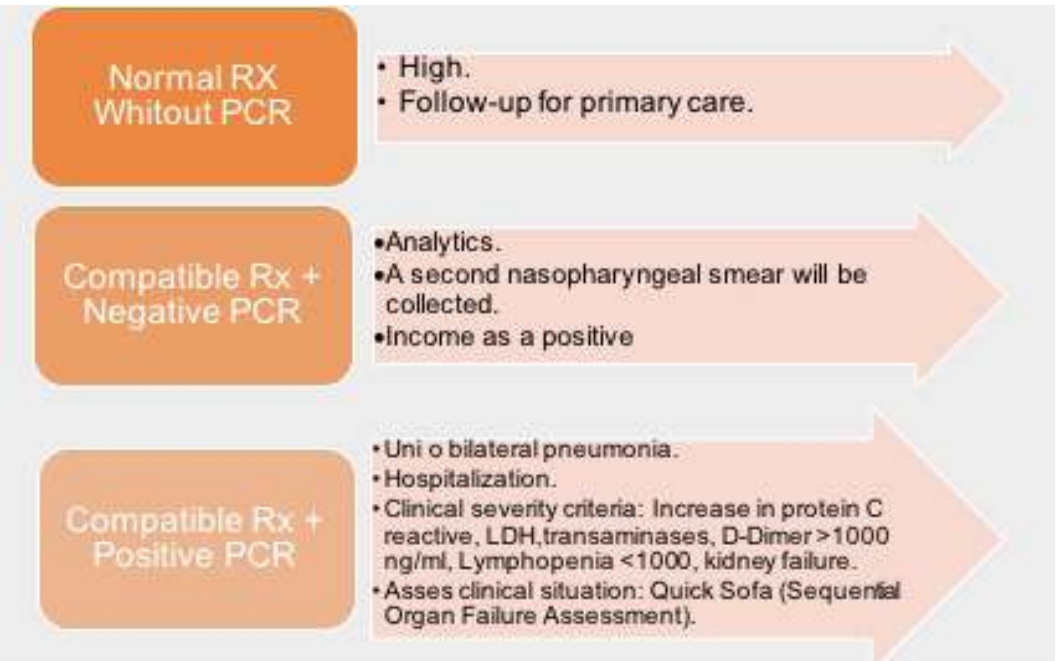
As it is known, the virus affects mostly the lung, as it has specific affinity for ACE2 receptors which mostly manifest in type 2 pneumocytes (15). From the first symptom to the onset of dyspnea, it takes about 5 days, and until the onset of Acute Respiratory Distress Syndrome (ARDS) about 10 days.

ARDS is a pathology that arises secondarily to a pulmonary or extrapulmonary injury, that occurs with patchy bilateral infiltrates which are not only due to cardiac pathology. It is characterized by loss of pulmonary elasticity (manifested by decreased compliance values) and ventilation/perfusion mismatch with heterogeneous involvement, coinciding collapsed areas with other hyperinflated ones. This was called “baby lung” (16), referring to the functioning of only a small fraction of the lung in the ARDS.

ARDS of patients with pneumonia by SARS-Cov-2 has some particularities, in fact, some recent reviews consider that the virus may occur in the form of two different ARDS phenotypes (17): the initial one, in which the lung is more compliant and there is less shunt, and another phenotype with a more fibrotic lung and with an important shunt (defined as PaO2/FiO2 <150 ratio), but also with a high dead space. In addition, it is characterized by a vascular disorder with a microthrombotic component, and another one which is secondary to the inflammatory response. Finally, it is important to highlight a problem of hypersecretion, with thick secretions that make it difficult to ventilate these patients.

Therefore, we believe that there would be different targets on which to focus treatment on patients with SARS-CoV-2 who need ICU admis-

Figure 1 - Situations of chest X-ray and its performance in the emergency department. April 2020.



sion; on the one hand, the treatment of respiratory failure and ARDS, and on the other hand, drug treatment (Figure-2). Details are described below.

5.1. Treatment of respiratory failure and ARDS

Depending on the clinical situation, we will assess the benefit of initiating non-invasive therapy, such as high-flow nasal cannula (HFNC) or non-invasive mechanical ventilation (NIV); these two procedures were initially discouraged due to their greater susceptibility to generate aerosols, but aerosolization is minimized by avoiding disconnections.

Another important issue is not to delay intubation if these therapies are not effective. In such cases, a "fast sequence" intubation will be necessary as follows:

5.1.1. Pre-oxygen with high FIO2. Avoid manual ventilation with mask and Ambu®.

5.1.2. Anesthetic induction with fast-acting drugs in appropriate doses.

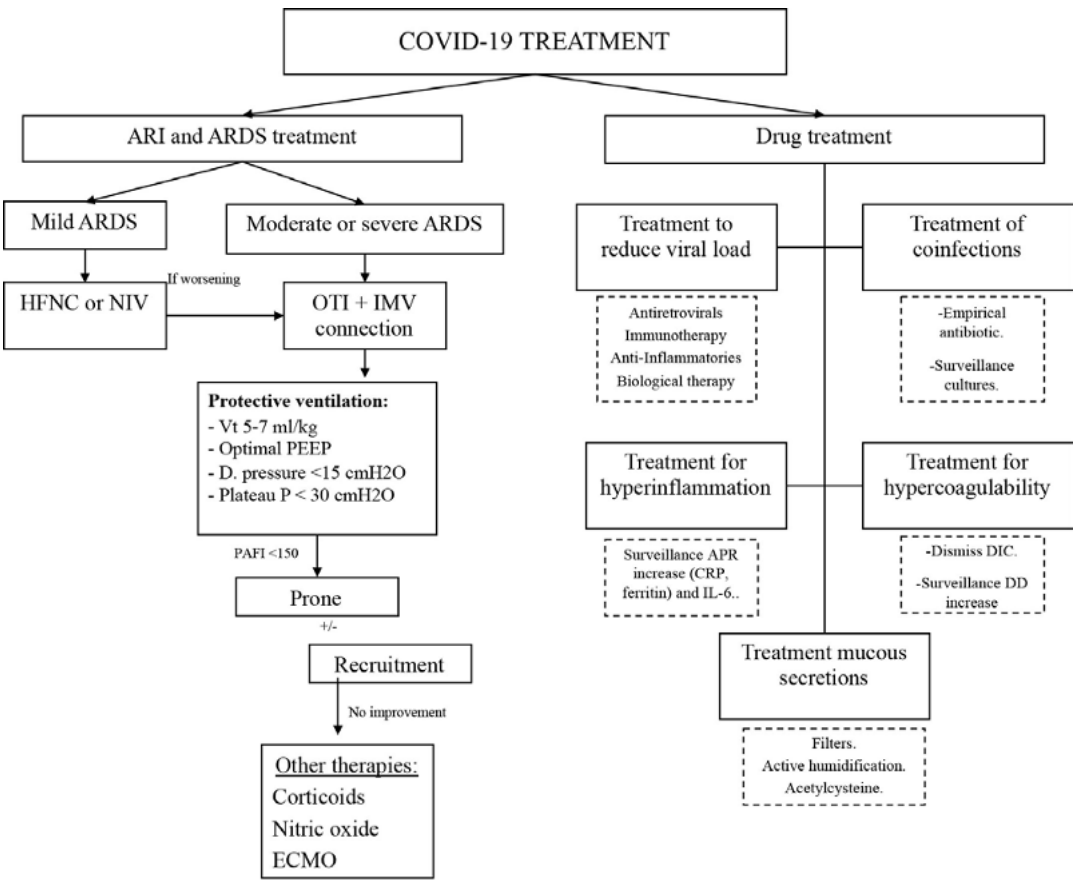
5.1.3. The procedure will be carried out by skilled personnel. The use of disposable devices has to be valuated; a difficult airway should be foreseen.

5.1.4. Tubes with subglottic suction and suction with closed system shall be used.

As a treatment of the ARDS, the following points stand out:

A. **Protective ventilation.** It consists of ventilating the patient avoiding ventilator-induced lung injury or VILI. To do this, **low tidal volumes (Vt)** must be ordered: Vt 5-7 mL/kg ideal. In addition, an **optimal Positive end--expiratory pressure (PEEP)** will have to be prescribed to the patient and his/her pathology. To do this, there are different strategies, but the most suitable is the one performed after pulmonary recruitment, looking for that PEEP

Figure 2 - Treatment of SARS-Cov-2.



that matches the best pulmonary compliance, taking as an optimal PEEP the sum of 2 points (2 cmH2O) plus that value that reflects the best compliance. Another protective ventilation strategy is to limit plateau pressures to values below 27 cmH2O and to achieve drive pressure values (DP-Plateau Pressure – PEEP) lower than 15 cmH20, as this last value estimates the transpulmonary pressure, and it is known that its decrease is related to better prognosis (18).

B. **Alveolar recruitment (AR).** It is defined as the re-expansion of previously collapsed lung areas by means of a brief and controlled increase in transpulmonary pressure. The idea of AR is creating and maintaining a collapse--free situation in order to increase the end-expiration volume and improve gas exchange (19). There are different strategies to follow, but the most used, describing it in a very simplified way, is the one based on PEEP increases of 5 to 5 cmH2O maintaining a fixed pressure drive with subsequent descent of the PEEP (to make an optimal PEEP calculation) looking for the best dynamic compliance (19).

C. **Prone decubitus.** It consists of putting the patient face down in a controlled and safe way. With this maneuver, transpulmonary pressures are homogenized and the dorsal areas, which are usually more collapsed and anatomi-

cally are the best infused, at being in prone position become more ventilated and recruited, improving the ventilation/perfusion (V/Q) ratio. In addition, it improves diaphragmatic mobility, decreases the weight of the heart on the lungs helping pulmonary expansion and improves hemodynamic, reducing the overload of the right ventricle (20, 21).

D. **Extracorporeal membrane oxygenation therapy (ECMO).** ECMO is a circulatory and respiratory mechanical assistance system which provides cardiac support for a short period of time as a bridge, in the case of respiratory support, until lung recovery or lung transplantation. It is a quick-start assistance through peripheral cannulation and it needs systemic anticoagulation. During ECMO therapy the respirator will be programmed in ultraprotective ventilation mode, to enhance the resting of the diseased lungs. It is essential that ECMO is established in experienced reference hospitals. The role of ECMO therapy in patients with COVID-19 is currently unclear (22).

5.2. **Pharmacological Treatment**

A. **Antiviral treatment.** It is thought that is paramount to lower the viral load, as it is related to greater inflammation, severity of the disease and higher mortality (23, 24). An indirect marker of the amount of viral load is the persistence of lymphopenia (24).

B. **Treatment of the state of hyperinflamation.** The reason for the use of these drugs is due to the belief that the underlying pathophysiology of significant organic damage in the lungs and other organs, is caused by an amplified immune response and the release of cytokines, also known as "cytokine storm" (15) or antibody-mediated immunopathology (25).

C. **Surveillance and treatment of coinfections.** Most COVID-19 patients in China received broad-spectrum empirical antibiotics, because it is difficult to distinguish this disease from other bacterial and viral pneumonias, and laboratory diagnosis of COVID-19 takes time (15). It is important to perform cultures and de-escalate when results are available. In addition, it is essential to rule out yeast infections such as Aspergillus, other viruses such as Cytomegalovirus, and bacteria such as *mycobacterium tuberculosis*, since both SARS-CoV-2 itself and the treatments administered can promote such infections.

D. **Surveillance of hypercoagulability state.** There is evidence that anticoagulant treatment improves prognosis in patients with high DD (26). Given that this treatment is not without risk, it is essential to rule out daily the occurrence of disseminated intravascular coagulation and, in patients with DD >6 times normal value, to assess anticoagulation if there is no contraindication.

E. **Treatment of mucous hypersecretion.** In patients who require orotracheal intubation, two high-efficiency filters (in the inspiratory and expiratory branches) will be placed as it allows the exchange of heat and humidity. In addition, treatment with intravenous acetylcysteine will be initiated in any patient who develops broncorrhea.

F. In Table-7, extracted from the Phua J et al. (15) some of the drugs most commonly used as anti-SARS-Cov-2 treatment are included.

6 - MORBIDITY AND LETALITY RATES

The patients at high risk to developing pneumonia are males, over 60 years, and those with a history of cardiovascular disease and DM.

Table 7 - Drugs most commonly used as anti-SARS-CoV-2.

Drug and Dosage	Target	References	Side effects
REMDESIVIR - 200 mg once daily in day 1. - 100mg once daily from day 2-10.	NUCLEOTIDE ANALOGUE Inhibits viral RNA-dependent RNA polymerase (RdRp)(15).	-Deemed to be the most promising candidate drug by experts convened in January, 2020, by WHO. -Effectively inhibited SARS-CoV-2, MERS-CoV, and SARS-CoV in vitro (15).	-Possibility of hypotension.
LOPINAVIR/RITONAVIR - 400 mg/100mg twice daily for up to 14 days. The timing of administration is during the early peak viral replication phase (initial 7-10 days).	PROTEASE INHIBITOR -It demonstrated in vitro activity against other novel coronaviruses via inhibition of 3-chymotrypsin-like protease (27).	-Second candidate identified for rapid implementation in clinical trials. -A relevant study shows that it is associated with reduced viral load and mortality in an observational study of SARS-CoV (15).	-Prolonged QT interval. -Gastrointestinal side-effects. -It is a CYP3A4 inhibitor.
HYDROXYCHLOROQUINE - 400mg twice daily in day 1. - 200mg twice daily from day 2. + **AZITHROMYCIN** - 500mg once daily.	ANTIMALARIAL -block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. -Immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells (27).	-Reduced SARS-CoV-2 load in the nasopharynx of patients with COVID-19, especially when combined with azithromycin (28). Despite these promising results, this study had several major limitations.	-Prolonged QT interval. -Seizures, -Hypoglycemia, -Neuropsychiatric effects, -Retinopathy.
INTRAVENOUS IMMUNOGLOBULIN - 400 mg/kg once daily for 3-5 days. In the first 7 to 10 days of infection, when viremia is at its peak and the primary immune response has not yet occurred (27).	IMMUNOTHERAPY	A study of human polyclonal immunoglobulin G (SAB-300) in a mouse model of MERS-CoV found reduced viral lung titers near or below the detection limit in mice infected with MERS-CoV (15).	-In IgA deficiency, risk of anaphylaxis due to anti-IgA antibodies.
CONVALESCENT PLASMA In the first 7 to 10 days of infection, when viremia is at its peak and the primary im- mune response has not yet occurred.	IMMUNOTHERAPY	In SARS-COV-2 is associated with reduction in viral load and improvement in fever, oxygenation, and chest imaging in a case series, but study limited by small sample size, multiple possible confounders, and absence of controls (15).	-Studies of SARS-CoV have not reported serious adverse events (15).
CORTICOSTEROID - Metilprednisolone 1mg/kg/día for 5-7 days, then progressive decrease in dose.	ANTI-INFLAMMATORY Decrease the host inflammatory responses in the lungs.	There is a wide divergence of opinion in the literature on whether corticosteroids should be used in patients with COVID-19, but there is no justification to deny the use of CST in severe life-threatening “cytokine storm” associated with COVID-19(29)	-Adverse effects, including delayed viral clearance and increased risk of secondary infection.
TOCILIZUMAB - 8 mg/kg or 400mg iv 1-2 doses.	MONOCLONAL ANTIBODY AGAINST INTERLEUKIN-6	Licensed for cytokine release syndrome; hypothetically work against cytokine storm with raised ferritin and interleukin-6 levels due to SARS-CoV-2 (15).	-Increase in upper respiratory tract infections (including tuberculosis) and other infections, hypertension, infusion related reactions, hematologic effects, hepatotoxicity, gastrointestinal perforations.

Early estimates of the lethality rate in Chinese series were around 2%. In Spain the Ministry of Health updates daily the epidemiological summary of confirmed cases of COVID-19 disease reported in Spain and other countries (30).

According to the information available so far, the lethality of COVID-19 in cases reported to REANVE - Red Nacional de Vigilancia Epidemiológica (National Epidemiological Surveillance Network) through the SiViES platform (Surveillance System in Spain) is 7.6% with a range from 0% for those under 15 years to 24.3% for those over age 80 years. A specific analysis of deaths shows that deceased patients, vs recovered patients, are significantly older (average age 82 vs 58 years), men are more represented, most often have underlying diseases, pneumonia and other respiratory complications, and more frequently have been hospitalized and admitted to ICU.

If we focus on critical patients, the Chinese series have a great variability, although in the subgroup of patients with ICU admission of the Guan WJ et al. (14) series, 2.3% required mechanical ventilation and 1.4% died.

7 - RETURNING TO WORK AFTER THE COVID-19 PANDEMIC

Recovering work activity is synonymous with quality of life, health and return to "normality"; on the contrary, its absence means one more duel to develop (31).

The WHO describes mental health as: "... a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community" (32).

After ICU admission, some patients develop Post-Intensive Care Syndrome. In addition to possible physical consequences as a result of the illness as well as the time spent in hospital, bedridden and drugs received, psychological consequences are also common during the first post-ICU year. The incidence of anxiety-related symptomatology is known to be 24%, depression is 28% and post-traumatic stress disorder (PTSD) may account for 22% (33). It is known that 64% of these patients return to work in the two years following the discharge and the quality of life perceived in them is much higher than those who remain unemployed (34).

All of this, in addition to the pandemic situation, makes it necessary to build a psychological support network for all those patients who have required hospital admission for COVID-19 disease and, moreover, for those who have required admission to ICU. Currently, some hospitals have implemented physical rehabilitation and early psychological support programs, initiating them during their stay in the critical care units (35).

CONCLUSIONS

The COVID-19 disease is currently a pandemic, therefore of worldwide interest for the entire population and posing a challenge for the health professionals in charge, especially those who are on the front line of health. As it is a new virus, there are many unknowns that occur both in diagnosis, management, treatment and subsequent follow-up of these patients. COVID-19 presents with symptoms of cough, fever, shortness of breath, nasal congestion, gastrointestinal symptoms, among others, which can progress to pneumonia and, in some cases, develop an adult respiratory distress syndrome, requiring admission to the intensive care. From primary care, the primary objective is to establish a diagnostic suspicion, generally to follow up by telephone within 24 to 48 hours from the time of the consultation and with surveillance 7 days after the evolution of symptoms, which is when complications occur in the majority of these patients. In hospital emergencies, when a patient suspected of COVID-19 arrives, depending on the clinical state (O2 saturation > or <95% and whether or not risk factors), the patient shall be subsidiary to the performance of additional tests for that diagnosis and therefore if is income or not; those hospitalized patients who present acute respiratory failure and bilateral pneumonia will require an ICU admission evaluation, and if it is assumed by the ICU, the different protocols will be applied according to the severity of the clinical picture.

CONFLICT OF INTEREST

None declared.

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The Psychosocial Impact of COVID-19 on health care workers

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ABSTRACT

At the end of 2019, a disease was identified, COVID-19, caused by a new type of easy and fast spreading virus, which led to the beginning of a worldwide pandemic. One of the most exposed groups to the virus and its psychosocial consequences is the healthcare workers, due to their implication in caring for affected people. Health workers are exposed to a fast and unpredictable situation that requires more human resources and materials than usual, however, the lack of means on account to this situation entails an increased probability of suffering different consequences, including the burnout syndrome, to which, generally, this professionals are already vulnerable. In addition, quarantine is added as a measure to prevent the spread of the pandemic, which is another handicap for healthcare workers. Quarantine means these professionals are more likely to suffer the foreseeable psychological consequences in general population, specifically, it has been observed that Post-Traumatic Stress Disorder (PTSD) is more prevalent, because of the stress load of the situation experienced.

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INTRODUCTION

A pandemic generates in human beings one of the most primitive answers at psychological level: fear. Fear is an emotion that allows us to react to a real or imagined event which we consider a threat, at the physical level as well as psychological or socioeconomic levels. Thus, fear guarantees our survival. As other emotions, fear activates the three levels of response in our body: cognitive, physiological and motor.

Fear is an emotion we experience as unpleasant, even though it is in and on itself functional, it becomes dysfunctional when it dominates our life, either our response exceeds the event we need to manage –our system generates a state of alert over something that could happen, anticipating and suffering the negative effects without actually happening–, or the event which we are exposed to is highly traumatic and exceeds our available resources, generating very high stress levels. This is when a disorder derived from anxiety occurs –

generalized anxiety disorder, panic disorder, agoraphobia– or stress –post-traumatic stress disorder (PTSD), complex PTSD, prolonged grief disorder. When a situation of fear and distress lasts, high levels take time to disappear. If we add other factors, such as loss of health, a loved one, job position or quarantine, post traumatic effects may last.

Although anxiety, depressive and distress symptoms can be found in high levels in general population, some groups can be more vulnerable than others to the psychosocial effects of pandemics. These would be people who contract the disease, those with high infection risk; people with preexisting medical, psychiatric, or substance use problems are at increased risk for adverse psychosocial outcomes; and, especially health care providers. This last group, considered essential workers, becomes both directly exposed to virus and to the psychosocial consequences derived from its propagation. They are particularly vulnerable, given their risk of exposure to the virus, concern about infecting and caring for their loved ones, shortages of personal protective equipment (PPE), longer work hours, and involvement in emotionally and ethically fraught resource-allocation decisions (1).

In fact, early research conducted on Chinese population shows that a significant proportion of health workers have depression symptoms (50.4%), anxiety (44.6%), insomnia (34%), discomfort (71.5%) (2). This evidence makes us consider highly relevant to focus on this population.

In this chapter we will describe the possible consequences at the psychological level in sanitary groups considering the different factors that affect the way they are facing this pandemic crisis.

Psychological consequences in healthcare workers

Labor health

During work performed by healthcare workers, several pressure elements from different sources may impact on keeping optimal conditions for a healthy working environment, and because of the saturation of the sanitary facilities due to the high level of virus infection, the health of these professionals has been obviously affected. We must not forget the efficiency and proper working order of these institutions depend mostly on its professionals' wellbeing, and the conditions in which they are performing their duties are putting at risk the physical and mental health of many of them as they are exposed to different stressors at work. Focusing on aspects related to occupational psychology, we can consider highlighting two groups of main factors which could influence on the possible psychological consequences caused by the pandemic in healthcare workers: lack of resources and heavy workload.

Lack of resources: This is a situation that all countries affected by the virus are facing, both material and human resources.

As for lack of material, a high percentage of professionals are getting infected for not having adequate personal protection equipment (PPE) and not using it properly, having to re-use in many occasions equipment which is only recommended for one-time utilization. To get an idea of this, at the beginning of the pandemic in Wuhan, virus transmission reached 29% of healthcare workers in hospitals (3), these high numbers decreased considerably when adequate protection steps were implemented. In Spain, one of the countries most affected by the pandemic, in April, according to Redacción Médica, three out of ten new infected people are healthcare workers (4), this shows the problem's magnitude. Besides the lack of PPEs, we must mention the lack of tests to identify possible cases in hospital professionals, in this way we can isolate tested positive workers to avoid virus propagation. All of this generates fear, uncertainty and insecurity in workers for not knowing if PPEs are protecting adequately and even if they could have the virus and not being aware of it.

Regarding the lack of human resources two elements must be considered. First, medical leaves due to the virus, which is directly related to the lack of equipment mentioned above. Second, the saturation of health institutions. According to data provided by Spain's Ministry of Health at the beginning of April:

In European Union and United Kingdom, in cases confirmed, 30% of persons with COVID-19 required hospitalization and 4% of these

were considered critical, defined as requiring mechanical ventilation, or other criteria to be provided with assistance in intensive care unit (ICU) (3).

In this context, it is evident there are not enough human resources to meet current demands, so medical institutions have signed contracts with doctors and nurses being in their last year of residency, as well as with medical graduates without specialization. This last group is formed by professionals who are mostly new in labor environment and might have been overloaded at psychological level because of the situations they have had to face since their little experience which is already a challenge for experienced professionals. The distress suffered in an unknown and new job for them, could generate a negative emotional association to this work environment, becoming an aversive stimulus to which they would not want to be exposed again.

Also, the working hours for many professionals have been modified, having to work more hours than usual, even making double shifts; time needed for resting to guarantee personal wellness and, therefore, a proper job performance. We must not forget fatigue is related to possible accidents, for example handling PPEs that increase the risk of infection. Additionally, the change of shifts could be a problem for family conciliation, increasing even more the pressure they are exposed to.

High volume workload: this factor is derived from the first one to a certain extent, but we have decided to take it into account independently as it is something health professionals normally deal with and previous studies have shown it is a factor that affects their health directly, especially in this situation.

Within work overload, there are two different types of overwork: quantitative, which relates to performing excessive tasks during working hours and, in this case, it is related to the saturation of health facilities which have required the reorganization of working days, thus generating physical as well as psychological exhaustion of professionals, as workers not having the opportunity to recover; and the qualitative overwork, defined as to having to cope with excessive demands on their cognitive as well as their emotional skills (5).

Both types of work overload contribute to worker's psychological discomfort but, considering our current situation, the qualitative overload plays a very important part in the consequences which will appear in healthcare workers in the middle term. The situation caused by COVID-19 could generate in workers a feeling of ineffectiveness and helplessness because of this qualitative overwork that they are facing, which in turn contributes to a high emotional load which is already affecting healthcare workers.

As we have said, if the factors described above last in time, they could generate different symptoms at psychological level in a population already predisposed for this type of problems. In fact, it is known that different levels of depression and anxiety are increasing progressively in healthcare workers and are above average of the general population, so it is assumed they could increase for the reasons explained before.

More precisely, one of the consequences caused by these stressors and to which healthcare workers are prone is the Burnout Syndrome (BS), defined as an excessive and prolonged stress whose main components are emotional fatigue causing energy loss, wear out feeling and fatigue; dissociation and, specifically, depersonalization, with regards to an individual's defense upon avoiding those emotions which cause discomfort; and diminish work performance, as work itself loses its previous value (6).

BS is declared by World Health Organization (WHO) as a labor risk affecting person's life quality, compromising individual's mental as well as physical health. Besides, at the organizational level, the worker with BS has not all the capacity to give his patients the healthcare they need, getting the quality of the health services even worse. BS can be identified using the following clinical evidence: social isolation, anxiety, fear, depression, anger, addictions, personality changes, guiltiness and self-immolation, changes in eating habits, substantial gain or weight loss, loss of memory disorganization, problems with concentration and sleep disorders (7).

Due to the effects caused by BS in worker's health at the individual level, as well as the re-

percussion on health system if it had, as it is expected, a high effect on healthcare workers, the prevention and treatment of BS and its manifestations would be essential for the physical and mental health care in these particular professionals, and the preservation of a high quality health system and attention to patients.

Quarantine

In addition to the labor conditions and its consequences quarantine is implemented to stop the expansion of pandemic. Recent history has had situations where quarantine was used as a measure to avoid expansion of contagious disease, such is the case for China and Canada during the outbreak of Severe Acute Respiratory Syndrome (SARS) or in some African countries during Ebola disease. Based on these, we know the psychological consequences caused by this type of isolation.

As stated by Liu, et al. (8) in their study, performed after the SARS pandemic in 2012, for the hospital workers, the post-traumatic stress and depression symptoms associated to the quarantine, can last up to three years after the crisis finalizes. Besides, they add, the healthcare workers placed in quarantine show greater symptoms of post-traumatic stress than the average population. Due to this fact, we consider particularly relevant to focus on this population.

In the systematic review launched by The Lancet (9), other research performed on healthcare workers active during SARS highlights that quarantine can produce a predisposition to suffer post-traumatic stress symptoms (10) or acute stress disorder (11). This disorder, according to ICD-10, is a disorder linked to Post-Traumatic Stress Disorder (PTSD) when an individual suffers in acute and temporary terms -minimum 2 days and maximum four weeks- the symptoms of anxiety as a reaction to an exceptional physical or psychological distress. This experience can be caused by indirect exposition, for witnessing events happening to other individuals, or by being informed about traumatic events that close people have suffered. Consequently, among others, it causes difficulty sleeping, irritation, poor concentration, motion disorders, hyper-surveillance, which could contribute to an increase in burnout.

The individuals with these disorders can show dissociative symptoms caused by the disconnection produced when trying to avoid anxiety by the upcoming event. This means that individuals could feel emotionally senseless or disconnected -as it occurs as consequence of BS-, suffer dissociative amnesia and, in the most severe cases, have the sensation that events are not real.

If not treated in time, the disorder or episode of acute stress could become a chronic PTSD, considered over time, or even a complex PTSD.

PTSD is a disorder, according to ICD-10 (12), characterized by 1) flashbacks or nightmares about the traumatic event which produce terror and strong physiological reactions, 2) avoidance of memories or thoughts related to the event, or to avoid activities, situations or persons related to, and 3) a lasting perception of a current noticeable threat. Due to these symptoms, professionals working in intensive care units (ICU) may not desire to keep working there. If these individuals develop post-traumatic stress, as a self-protection strategy either being aware or unaware, they may not want to return to where it was produced.

Therefore, the psychological consequences derived from the social situation to which the healthcare workers are exposed could not only have implications at individual level, but also increase the burnout already mentioned and may help degrade the health system institution; due to the fact that having professionals with PTSD would decrease human resources either with sick leaves or for not being able to cover certain health services.

CONCLUSION

Human beings in general have a great resilience capability and adaptability to circumstances. However, as it is known, we require help from other persons to facilitate these processes. It is necessary to consider the skills that healthcare workers require to develop to be able to overcome the circumstances derived from the COVID-19 pandemic, as it has caused a considerable increase in the stress levels they are normally exposed to.

The recommendations published by World Health Organization (13) include one section dedicated exclusively to healthcare workers, where it has suggestions to reduce the impact of the BS consequences described. Besides, another section is specifically focused in one of the consequences of BS: social isolation. The human beings need of counting on others' support, the relevance shown by WHO, added to what has been written in this article, make us consider social isolation for workers of health institutions as a special relevant variable.

As explained, BS has as consequence, generally speaking, social isolation, if we add to this the specific circumstance of quarantine as a measure to stop COVID-19 expansion, and the fear of these workers to infect their loved ones; we face a social isolation higher than expected. Besides, as we have seen, quarantine causes PTSD –especially in this group–, which increases the chances of BS to develop. This scenario could be generating a feedback cycle, developed by social isolation, which requires maximum attention.

Certainly, most of the countries affected by this pandemic, as a result of WHO recommendations, have provided answers to the needs of mental health care. According to these recommendations, psychological assistance to general population becomes highly essential and particularly, to healthcare workers during the pandemic and, at least, up to three years after the event, as highlighted by Liu, et al. (8).

Some experts suggest strengthening the mental health systems and performing stepped care, which means performing, at the beginning, a treatment low in system resources based in stabilization and self-management of patients in need of this attention so as to, when demand decreases, invest more resources and meet the needs of every patient (14).

ABBREVIATIONS

PTSD = Post Traumatic Stress Disorder

CONFLICT OF INTEREST

None declared.

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Emergency Surgery in Urology during the COVID-19 Pandemic

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ABSTRACT

Proposal: To highlight the indications for emergency surgery during the 2019 Coronavirus pandemic (COVID-19) that support recommendations published in mid-March 2020 by the American Confederation of Urology on its website.
Materials and Methods: A bibliographic search was conducted in PubMed and Cochrane Library to perform a non-systematic review, using key words: Urology, Emergency and COVID-19, to determine recommendations for patients that should receive emergency care due to urological pathology.
Results: The main recommendations and protocols in the management of different urological emergencies during the COVID-19 pandemic are reviewed and discussed.
Conclusions: We are living a new condition with the COVID-19 pandemic, which obliges urologists to conform to the guidelines that appear on a daily basis formulated by multidisciplinary surgical groups to manage urological emergencies. Consequently, in this time of health crisis, we must adapt to the resources available, implementing all biosecurity measures to protect patients and all health personnel who are in charge of patient management.

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INTRODUCTION

The World has changed since the beginning of December 2019, when the city of Wuhan, China, identified the first case of an atypical pneumonia produced by a Coronavirus, which is now known as COVID-19. From that first case to date, the disease has had exponential growth, and the World Health Organization has classified it as a true pandemic (2). Up to May 15, 2020 (3), this disease has spread across more than 185 countries, affected more than 4,400,000 people, and killed more than 300,000 patients worldwide. The southern hemisphere is currently entering the winter season and is seeing an overwhelming upsurge of reported cases in this part of the planet.

This avalanche of cases has saturated the health systems of most countries, where a large number of patients have been reported, which

has forced changes in the dynamics of hospitals. We are currently seeking solutions to optimize resources, restructuring spaces so that we can absorb patients that we potentially know have a great chance of transmitting the disease to other patients and to all the health personnel who are providing care; this may be aggravated in some places by the restriction or lack of personal protective equipment (4).

Most emergency services are full of patients, many of them with great need to be admitted to these hospitals. For this reason, operating structures of hospitals have been transformed and rooms have been filled with COVID 19 patients.

The need for beds and mechanical ventilators in intensive care units has increased due to the influx of critical patients requiring ventilatory support, transforming surgical areas into intensive care spaces, decreasing the capacity of surgical areas. On the other hand, it has been shown that patients and families who are coming to these hospitals with COVID 19 patients have increased the risks of being infected with this pandemic.

The large influx of patients in many places has forced urologists to actively participate in emergency services to support the care of COVID patients 19.

This has resulted in the need to postpone the care of pathologies of urology patients considered non-urgent. Scientific societies and institutions have made a number of recommendations that should be addressed as a matter of priority.

Urologists as well as all health personnel are forced to redefine our practice in consultation and emergency services, leading to the search for patient care protocols.

The intention of this review is to standardize which pathologies need emergency surgical care during this Covid 19 pandemic.

OBJECTIVE

To highlight the indications for emergency surgery during the COVID 19 pandemic that support recommendations published in mid-March 2020 by the American Confederation of Urology (Table-1).

MATERIALS AND METHODS

A bibliographic search was conducted in PubMed and Cochrane Library to perform a

Table 1 - American Urology Confederation (CAU) Position in the Surgical Management of Urologic Cases in COVID-19 Pandemic.

American Urology Confederation's position in the surgical management of urological cases during COVID-19 pandemic	
First Recommendation	Social Distancing Hand washing Fragile Patient Protection
Genuine Emergency	Renal colic, renal collections or abscesses, acute urinary retention, Fournier gangrene, Penis or testicle fracture, testicular torsion
Absolute Oncologic Emergency	Cystectomy, nephrectomy, TUR (high risk), high risk prostatectomy, orchiectomy, nephroureterectomy
Non-oncologic Emergency	Emergency lithiasis, hematuria with clot retention,
Relative Oncologic Emergency	Prostate biopsies, intermediate or low risk prostatectomy.
Non-emergencies	Scrotal surgery, cystoscopy, andrology surgery, brachytherapy, functional and reconstructive surgery, lithiasis elective surgery, HPB surgery.

non-systematic review, using key words: Urology, Emergency and COVID 19, to determine recommendations for patients that should receive emergency care due to urological pathology.

RESULTS

Taking into account lessons learned from China, Italy, and other countries, in the coming weeks, rates of COVID-19 in the southern hemisphere are expected to start soaring and peaking at the end of May and June; there will be variability in rates, peaks, and times, and though we cannot predict what will happen at this point, we should all be preparing.

Accordingly, we are still recommending surgeons to reduce elective surgical procedures (5).

The American College of Surgeons has published a series of triage recommendations that guide the selection of non-emergency surgical procedures in COVID-19 patients (6) (Table-2).

Guidelines for triage of cancer patients

Once the COVID 19 pandemic is confirmed, Hospital Centers and health personnel in charge of treating cancer patients should establish criteria for treating these patients based on criteria that have been defined by the American College of Surgeons. These criteria should be in relation to the availability of resources of the different centers: hospital and ICU beds, respirators, blood transfusion capacity and personal protective equipment, for patients and for all health personnel in charge of patients with this condition.

It is advisable so that only high-risk patients should be treated, advising hospitals to discontinue elective surgeries (6).

Oncological pathology

Oncology patients have to visit hospitals because they have to receive treatment or be monitored for their disease, and they may be immunocompromised due to their malignant neoplasm

Table 2 - Elective Surgery Acuity Scale (ESAS).

Tiers/ Description	Definition	Locations	Examples	Action
Tier 1a	**Low acuity surgery/ healthy patient** Outpatient surgery Not life threatening illness	HOPD ASC Hospital with low/no COVID-19 census	Carpal tunnel release Penile prosthesis EGD Colonoscopy	Postpone surgery or perform at ASC
Tier 1b	**Low acuity surgery/ unhealthy patient**	HOPD ASC Hospital with low/no COVID-19 census		Postpone surgery or perform at ASC
Tier 2a	**Intermediate acuity surgery/healthy patient** Not life threatening but potential for future morbidity and mortality. Requires in hospital stay	HOPD ASC Hospital with low/no COVID-19 census	Low risk cancer Non urgent spine Ureteral colic	Postpone surgery if possible or consider ASC
Tier 2b	**Intermediate acuity surgery/unhealthy patient**	HOPD ASC Hospital with low/no COVID-19 census		Postpone surgery if possible or consider ASC
Tier 3a	**High acuity surgery/ healthy patient**	Hospital	Most cancers Highly symptomatic patients	Do not postpone
Tier 3b	**High acuity surgery/ unhealthy patient**	Hospital		Do not postpone

or their cancer treatment, which puts them at risk of contracting infections and seems to have a higher risk of contracting COVID 19 than the general population.

Patients should be guided regarding hand hygiene measures, social distancing, use of personal protective equipment, and should be taught about symptoms and signs of the disease.

The need to carry out or postpone an active intervention must be individualized in low--risk patients and must be considered on a case--by-case basis.

Visits to hospital centers should be minimized and telemedicine programs should be incorporated to reduce the exposure risk (7).

In a study of 1,524 patients admitted to the Department of Radiation and Medical Oncology, in the Zhongnan Hospital of Wuhan University, from December 30, 2019 to February 17, 2020, it was revealed that cancer patients had a double risk of infection by COVID 19 compared to the general population (8).

The American Confederation of Urology has published on its website recommendations that oncological surgeries should be considered Genuine Emergencies: Cystectomy, Nephrectomy, Nephroureterectomy, Prostatectomy and TURB, all high risk and Orchiectomy for testicular tumor (Table-1).

The following were also considered as relative Oncological Emergencies: Prostate Biopsies, Prostatectomies of intermediate or low risk.

Management of Lithiasis in the COVID 19 period

Management of renal colic should be done conservatively to the extent possible.

Patients who have a proven diagnosis of COVID 19 or who are highly suspicious and who need to undergo an endourology procedure should be managed in dedicated operating rooms, in negative pressure environments, ideally with regional anesthesia and if they need anesthesia machines, these should be used only for COVID 19 cases (9).

Despite the fact that lithiasis disease is considered a benign disease, many patients may present cases of renal colic resistant to medical treatment and many may be complicated by severe septic conditions, which may require emergency surgery (10).

We can consider urgent situations in patients, who have the following conditions, related to lithiasis disease, that require emergency surgery: solitary kidney, acute kidney failure, bilateral obstruction, colic that is resistant to medical treatment, and kidney stones or infected ureteral.

We must not forget that patients, despite having decompressed the urinary tract, administered antibiotics and other support measures, 15% will need to enter intensive care units, places today where the beds are full of patients with COVID 19 and that despite all the care, mortality will range between 8-10% (10).

Other emergency conditions

There are several urologic emergency conditions that we will describe one by one.

Acute Urinary Retention: If possible, the urethra should simply be catheterized or, in its absence, a retropubic cystostomy should be performed. At this time of the COVID 19 pandemic, prostate surgery for benign pathology should be considered a non-emergency. In the case of patients with severe hematuria, this will be discussed in the section related to this condition (11).

Severe Hematuria: In the event that the patient presents severe hematuria, the cause must be identified, possible coagulation disorders should be studied, a urethral catheter should be placed and the bladder should be irrigated. If nevertheless hematuria persists, an endoscopic examination should be performed, fulguration of active sites of bleeding, and eventually perform endoscopic resections of bladder or prostate tumors, trying to minimize hospital stay.

Genitourinary Trauma: Patients suffering from trauma to the genitourinary tract should be evaluated and classified; assessing hemodynamic stability and severity of hematuria; stable renal trauma should be managed conservatively and if stable should be done on an outpatient basis; patients with severe bleeding or leaks should be managed with endovascular procedures and / or ureteral

catheters. Hemodynamically unstable patients, with penetrating, V-degree injuries, pulsating or expanding hematomas, should be explored (12).

Fractures of the penis and testicles should be explored immediately with closure of the tunica albuginea in the first case, and trying to preserve as much viable tissue as possible, in the second case. These patients should be managed on an outpatient basis (12).

Acute Scrotum: It must be surgically intervened immediately, untwisting the affected testicle and, if this is feasible, bilateral orchiopexy should be performed, failing that, orchiectomy of the affected gonad. These must also be outpatient procedures (13).

Scrotal masses: They must be drained on an outpatient basis and healing must be performed at home, with the idea that they be resolved by second intention.

Fournier Gangrene: It is a true urology emergency that must be resolved by extensive debridement within 24 hours of its presentation and by administering broad-spectrum antibiotics, preferably performing procedures with spinal blocks and home cures (14).

CONCLUSIONS

We are experiencing a new condition with the COVID 19 pandemic, which forces us urologists to comply with the guidelines that appear daily formulated by multidisciplinary surgical groups, to manage urological emergencies, and we must adapt to the available resources, implementing all the measures of biosecurity to protect patients and all health personnel who are in charge of patient management, in these times of health crisis.

CONFLICT OF INTEREST

None declared.

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Impact of Covid-19 on the urology service in United States: perspectives and strategies to face a Pandemic

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ABSTRACT

Over the course of several weeks following the first diagnosed case of COVID-19 in the U.S., the virus rapidly spread across our communities. It became evident that the pandemic was going to place a severe strain on all components of the U.S. healthcare system, and we needed to adapt our daily practices, training and education. In the present paper we discuss four pillars to face a pandemic: surgical and outpatients service, tele-medicine and tele-education. In the face of unprecedented risks in providing adequate health care to our patients during this current, evolving public health crisis of COVID-19, alternative patient management tools such as telemedicine services, allow clinicians to maintain necessary patient rapport with their healthcare provider when required. As a subspecialty, urology should take full advantage of telehealth and tele-education at this juncture. As tele-urology and tele-education can obviate the potential drawbacks of "social distancing" as it pertains to healthcare, the platform can also reduce the risk of COVID-19 spread, without compromising quality urological care and educational efforts. Telehealth can bring urologists and their patients together, perhaps closer than ever.

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INTRODUCTION

The novel coronavirus known as severe acute respiratory syndrome corona virus-2 (SARS--CoV-2) has rapidly spread across the globe causing a pandemic known as the Coronavirus Disease 2019 (COVID-19) (1) . On March 11, 2020, the World Health Organization (WHO) defined COVID-19 as a pandemic, and two days later, the President of the United States (U.S.) declared the COVID-19 outbreak a national emergency.

Since the first reported case in the U.S. (2), the healthcare community had been bracing for possible community spread of COVID-19 and its potential impact on the U.S. healthcare system. The U.S. was warned of what to expect by our healthcare colleagues across the globe, especially in Italy, where the virus' impact had been felt several

weeks earlier than the U.S. (3). As in Asia and in some European countries, widespread transmission of COVID-19 in the U.S. was likely to occur with the majority of the U.S. population becoming exposed to the virus and potentially contracting COVID-19.

Over the course of several weeks following the first diagnosed case of COVID-19 in the U.S., the virus rapidly spread across our communities. It became evident that the pandemic was going to place a severe strain on all components of the U.S. healthcare system, and we needed to adapt our practices quickly to allow us to care for a surging number of COVID-19 positive patients. According to the Centers for Disease Control and Prevention (CDC), more cases of COVID-19 are likely to be identified in the U.S. in the next weeks, requiring stricter measures to reduce community spread. Moreover, the pandemic is placing a heavy demand on resources such as personal protective equipment (PPE), intensive care unit (ICU) beds, ventilators, medical supplies, as well as appropriately trained health care professionals. It became obvious that healthcare systems needed to reorganize to avoid being overwhelmed.

Impact of COVID-19 on the surgical service

On March 18th, 2020 the Centers for Medicare & Medicaid Services (CMS), a federal agency within the U.S. Department of Health and Human Services, formally released recommendations to delay all elective surgeries and non-essential procedures. In response, professional bodies began to make recommendations to help in re-prioritizing surgical cases and healthcare systems began to create an individualized plan for their institution to prepare for a surge in COVID-19 cases and how they would meet the challenges (4).

Urologists across the U.S. began deferring elective procedures and triaged their surgical cases (5, 6). Publications addressing management of genitourinary cancer care as well as kidney stone patients during the COVID-19 pandemic have helped guide our care of the urologic patient (3, 7). It is important to delay non-urgent cases not only to conserve medical resources but also to protect our patients as well as healthcare workers from potentially being exposed to COVID-19. In the worst hit regions of the U.S. such as New York, urologists were redeployed to assist with care of COVID-19 patients (8, 9). But even for those who are not redeployed to the emergency room and ICU, there are several additional preoperative considerations when operating during the COVID-19 era. The surgeon must weigh the risks to the patient from their underlying disease necessitating surgery versus the risk from possible COVID-19 exposure. A significant population of urologic patients are older with multiple comorbidities, placing them at a greater risk of worse outcomes if they were to contract the novel coronavirus (10). Those patients with genitourinary malignancies face even greater risk than their age matched cohort, as cancer patients are noted to have higher risk and more severe outcomes in a study from China (11). There is a national shortage of blood products during this pandemic and one must be judicious with transfusing their patients as well as weight the need for blood products during the perioperative period when considering proceeding with a surgery (12). As studies have indicated, a significant portion, up to 60% of patients whom are infected with COVID-19, may display minimal to no symptoms, yet be contagious and further spread the virus (13). It is prudent to screen every patient scheduled for a surgical procedure with not only with a comprehensive history and physical exam, but also with COVID-19 screening 1-3 days preoperatively to identify potential asymptomatic carriers and consequently delay their procedure as these patients are shown to have a 20% mortality rate if undiagnosed and undergo surgery during the incubation period (14).

Patients that need urgent surgeries are brought to the operating room (OR) with stringent rules and restrictions in place to mitigate the spread of COVID-19. Specific PPE guidelines have been adopted across U.S. hospitals to appropriately resource the insufficiently available masks and gowns while protecting their clinicians and staff. Aerosolizing procedures such as intubation require N95 masks with face shields for all non-COVID positive patients, while a Powered Air-Purifying Respirator (PAPR) is required for all COVID-19 po-

sitive patients (15). All staff except for the anesthesia team are asked to step outside the OR for intubation as well as extubation to minimize exposure risk. In addition, for those patients whom are suspect or have tested positive, staff should remain outside the room for at least 18 minutes to remove 99% of aerosolized virus in a negative pressure room (assumes ACH 15/hr) (16). Urologists must be aware that the virus is shed not only during aerosolizing procedures, but can also be shed in blood, urine and feces (17). During laparoscopic and robotic procedures, there is a theoretical risk of aerosolizing the virus therefore caution must be taken to suction gases into a closed system during de-sufflation of pneumo-peritoneum, and the OR staff must wear N95 masks throughout the case to limit possible exposure (18). For those performing robotic surgeries, surgeons should consider donning masks and gloves at the surgical console to minimize the exposure to COVID-19. It is critical for teaching institutions to protect their trainees and limit exposure during this COVID-19 pandemic. Academic institutions have modified and restructured their training programs to minimize exposure to their residents and fellows, as well as avoid any non-essential personnel such as visiting urologists, medical students, and researchers in the OR (19).

Post-operative care of our patients is also different during the COVID-19 era as entire hospital wards have been transformed to care for COVID patients. Urology patients are placed on non-COVID floors, but in some cases, this can lead to ancillary care provided by nurses not familiar with the management of a post-operative urology patient. Hospitals across the U.S. have adopted stern policies limiting any patient visitors per CDC recommendations and this has led to our surgical patients unable to have visitors during their hospital stay (20) . Further, the patient care team must carefully weigh the need for post-hospitalization rehabilitation for our patients as placement to nursing homes and long-term care facilities can subsequently place them at a higher risk of contracting COVID-19. Additionally, it is critical to inquire about our patients after discharge regularly either via phone call or telemedicine to confirm an uneventful recovery while convalescing at home to help minimize possible readmissions.

Impact of COVID-19 on the outpatient service

No facet of the U.S. healthcare system has been spared by the COVID-19 pandemic and outpatient services are no different. As we continue to make every effort to mitigate the spread of the virus, it is important to maintain social distancing, even within the hospital and outpatient clinics. As healthcare systems began to restructure and organize their resources and personnel to prepare for a surge in COVID-19 patients, outpatient visits were reduced to only those deemed absolutely necessary while all others were switched over to the rapidly adopted telemedicine platform. On March 17, 2020 CMS announced it had lifted restrictions on billing for telemedicine visits facilitating the wide adoption of telehealth during the pandemic (21). Minimizing traffic at the outpatient clinics allowed for appropriate social distancing, medical resource conservation, and limiting exposure risks to patients and staff alike. Based on CDC guidelines, patients checking in for in-person visits were screened for any symptoms of COVID-19 over the phone at the time of scheduling their appointment as well as upon arrival to the facility and are provided with a mask at check-in to mitigate the spread of the infection (22). All front and back office staff should wear masks and PPE as indicated by CDC guidelines to minimize any exposure. While most office visits were changed to telemedicine visits, there are patients still requiring clinic procedures and in-person visits. Recommendations for triaging office procedures have been made by Katz et. al as well as Howard et. al. to help guide the efforts to limit any non-urgent procedures (5, 23). While this transition away from in-person clinic visits has presented new challenges for the provider and the patient, the U.S. healthcare community has risen to meet these demands with some changes likely to stay in place beyond the COVID era.

Impact of COVID-19 on Telemedicine

Following the concept and step-wise restrictions of *#Stayathome* mandates, millions of

Americans have had to restrict their daily activities, avoiding public areas, public transportation, and reduce physical contact to limit the risk of person-to-person transmission. Under these circumstances, telehealth represents the venue for reaching these goals without limiting access to healthcare or compromising patients' health unduly. The concept of the tele-visit employs telecommunication tools to share healthcare information between patients and providers. Several communication tools have been described for two-way audio-video platforms such as computers, touchpads, and smartphones (24).

According to a 2019 survey, only 10% of Americans have used telehealth for a virtual consultation with lack of access (34.6%) and poor awareness (39.7%) of telehealth options as the primary hurdles to adoption (25). The COVID-19 outbreaks and the restrictions suggested by the CDC with stepwise implementation by government agencies for containing the spread of contagion would ultimately bring telehealth into the mainstream of practices, thereby reshaping the future of access to healthcare. In this setting, tele-urology could provide an alternative setting to evaluate post-operative patients. The tele-visit would make it easier for patients and providers to connect, while reducing person-to-person contact with public transportation, in various waiting rooms, hospitals, and clinics, including the urologist and their staff.

Patient acceptance and perceptions of telehealth for new patient visits, follow-up visits, clinic, and hospital consultations have been previously explored, showing potential for improving the urologic continuum of care. Younger patients (mean 62 vs. 65 years), higher education level (77% vs. 65%), previous exposure to video--conference tools (57% vs. 38%), those travelling longer distances (>90 min; 69% vs. 58%), and days missed from work (>1 day; 39% vs. 29%), have been found to prefer the tele-visit setting for sharing new symptoms and sensitive information (26). Viers et al. reported the use of tele-visits for patients following prostatectomy. No significant differences were found in patient perception of the quality of care nor satisfaction with the visit, with similar patient-to-provider face time (14.5 min vs. 14.3 min), patient wait time (18.4 min vs. 13.0 min), and total time devoted to care (17.9 min vs. 17.8 min). Likewise, there were no differences with the urologists' perspective. Further, overall costs to patients have been found to be lower with the tele-visit (27).

While tele-urology showed encouraging results, up until now it had only been offered as an option. In our current pandemic setting with increasing spread of the COVID virus and mobility restrictions, it might be necessary to employ telehealth to maintain patient access to healthcare. As regulatory barriers for the use of telehealth systems have been tabled for now, urologists should take the opportunity to attest to the viability and benefit of telehealth. Web-engine queries for "telehealth" have increased in the past months, paralleled with the increasing searches for Coronavirus information (Figure-1), these trends cannot be ignored as they are beneficial in promoting a new age of productive healthcare delivery options. At the USC Institute of Urology, we started our telehealth program in 2017. Details of the tele-visit flowchart are reported in Table-1.

Impact of COVID-19 on Tele-Education

In the COVID-19 era, there has been an increase demand for educational opportunities as clinical volume has slowed. The American Urological Association (AUA) has previously established an online Core Curriculum, which is updated regularly and available to all AUA members. However, new challenges have risen in medical education with the limits in place due to social distancing. Regional and national conferences have been cancelled, including the AUA Annual Meeting. In response, the AUA has published not only the abstracts from the meeting, but also the surgical videos to enhance virtual learning. A webinar program, AUA Live, is being developed as well.

While virtual learning is being increasingly used in post-graduate medical education, it has been a mainstay of many medical school programs for years, especially during the pre-clinical curriculum (28). Many students have preferred the flexibility of recorded lectures in lieu of large

Figure 1 - Google trends analysis for "Tele-Health OR Telehealth" and Corona Virus. Data are reported in relative search volume.

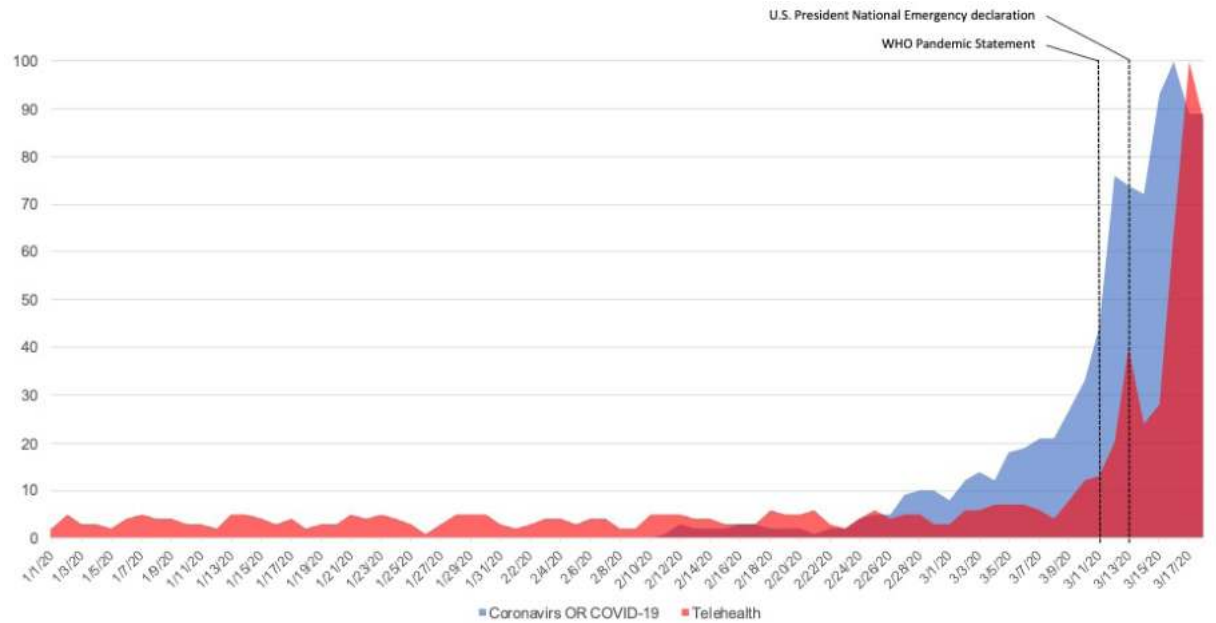

Table 1 - Tele-visit flowchart.

1. First, patients are selected by symptoms and disease and reason for the clinical consultation (urgent vs routine),
2. A phone call to patients to triage who can be evaluated using the tele-visit tools and who needs a physical evaluation and / or imaging and /or instrumentation.
3. Hardware (laptop, personal computer, smartphone or touchpad), software (specific HIPPA compliant tele-health or tele-conference call software) and connectivity for the video visit are required in order to set up the tele-visit appointment.
4. When setting up the tele-visit, the support staff needs to provide all the technical information necessary for a telehealth appointment
5. For new patients, previous health records need to be provided and outside imaging and tests downloaded into the EMR
6. At the time of the telehealth visit an appropriate environment is important to keep the privacy of the patient.
7. At the time of tele-visit, the physician needs to first verify patient's information and obtain verbal consent for the visit. The consent should include purpose and nature of consultation, voluntariness, benefits and risks (*including potential loss of confidentiality*) and potential need for subsequent in-person face to face visit. It is important giving the patient alternatives to tele-visit and notify the patient that other healthcare professionals (including students, residents, and technical personnel) may be involved in the audio-video evaluation.
8. Make sure that patient and physician are online during the entire tele-visit, and fix eventual technical failures in due course.
9. After the visit, the Urologist should document all the information obtained in the medical records. Complete documentation in the medical record of all virtual or phone visits must include:
   - ✔ the reason for the visit
   - ✔ history of present illness
   - ✔ observations/objectives
   - ✔ the assessment and plan for the patient
   - ✔ confirmation of verbal patient consent

in-person lecture halls. However, post-graduate medical education is more traditionally in-person, with clinical experiences, teaching conferences, grand rounds, and morbidity and mortality conferences (29). Now, conferences and presentations have been shifted to virtual formats. Trainees are often included in telehealth visits to maintain their clinical exposure. Surgical residents cannot replace their operative experience, but some are able to augment their learning with simulators (30). Several surveys have been distributed to assess the impact of COVID-19 in urological training, in particular. A questionnaire sent to all Italian urology residents found that on-call activity was not significantly changed, but there were dramatic reductions in outpatient visits and diagnostic procedures for residents at all levels. Senior residents had compromised volumes of surgical procedures (31). A U.S. based survey from the University of Texas, Houston, is pending publication of these results. A survey of urology residents from 58 countries reported that the preferred educational content included guideline updates and surgical videos. The European Society of Residents in Urology published educational alternatives to compromised activities. For example, to temporarily replace surgical activity, the European Association of Urology education section has online courses, surgery videos, and webinars, and the Surgery in Motion School has videos of surgical demonstrations (32).

To address the demand for high-quality education, a number of programs have started online lecture series. Several institutions have publicized their previously internal lectures, while others have created brand new programs. With the increased usage of tele-conferencing applications, inviting speakers from across the country, and even internationally, has become easier to organize and promote. Moreover, these lectures are readily available to those in practice and not solely limited to trainees within academic institutions. A list of publicly available cost-free lecture series is included in Table-2.

Table 2 - List of available free lecture series.

Institution/Group	Name	Link
Urology Institute at University Hospitals/ Case Western Reserve University and SUNY Upstate	Genitourinary Reconstruction Online Learning Series	https://www.uhhospitals.org/medical-education/urology-medical-education/urology-residency/overview/online-learning-series
Educational Multi-institutional Program for Instructing REsidents (EMPIRE)	Urology Lecture Series	https://nyaua.com/empire/
Memorial Sloan Kettering Cancer Center	Science Spotlight	https://www.mskcc.org/research/ski/education-training/sciencespotlight
National Cancer Institute, Urologic Oncology Branch	Urologic Oncology Grand Rounds	https://twitter.com/NCICCR_UroOnc
Society of Women in Urology	TeleURO AFRICA 2020	https://swiu.org/swiu-news/teleuro-africa-fpmrs.aspx
University of California, Irvine	Grand Rounds	http://urology.uci.edu/education_grandrounds.shtml
University of California, San Francisco	Urology Collaborative Online Video Didactics (COViD)	https://urologycovid.ucsf.edu/
University of California, San Francisco	Pediatric Urology Fellowship Lectures Online (PedsUroFLO)	https://pedsuroflo.ucsf.edu/
University of Southern California	Urology 60 Minutes	https://www.youtube.com/channel/UCuOf9gTZLObAM7HXHdUSA_Q

CONCLUSIONS

In the face of unprecedented risks in providing adequate health care to our patients during this current, evolving public health crisis of COVID-19, alternative patient management tools such as telemedicine services, allow clinicians to maintain necessary patient rapport with their healthcare provider when required. As a subspecialty, urology should take full advantage of telehealth and tele-education at this juncture. As tele-urology and tele-education can obviate the potential pitfalls of "social distancing" as it pertains to healthcare, the platform can also reduce the risk of COVID-19 spread, without compromising quality urological care and educational efforts. Telehealth can bring urologists and their patients together, perhaps closer than ever.

CONFLICT OF INTEREST

None declared.

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LECTURE

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Laparoscopic and robotic urology surgery during global Pandemic COVID-19

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ABSTRACT

Known laparoscopic and robotic assisted approaches and techniques for the surgical management of urological malignant and benign diseases are commonly used around the World. During the global pandemic COVID-19, urology surgeons had to reorganize their daily surgical practice. A concern with the use of minimally invasive techniques arose due to a proposed risk of viral transmission of the coronavirus disease with the creation of pneumoperitoneum. Due to this, we reviewed the literature to evaluate the use of laparoscopy and robotics during the pandemic COVID-19. A literature review of viral transmission in surgery and of the available literature regarding the transmission of the COVID-19 virus was performed up to April 30, 2020. We additionally reviewed surgical society guidelines and recommendations regarding surgery during this pandemic. Few studies have been performed on viral transmission during surgery. No study has been made regarding this area during minimally invasive urology cases. To date there is no study that demonstrates or can suggest the ability for a virus to be transmitted during surgical treatment whether open, laparoscopic or robotic. There is no society consensus on restricting laparoscopic or robotic surgery. However, there is expert consensus on modification of standard practices to minimize any risk of transmission. During the pandemic COVID-19 we recommend the use of specific personal protective equipment for the surgeon, anesthesiologist and nursing staff in the operating room. Modifications of standard practices during minimally invasive surgery such as using lowest intra-abdominal pressures possible, controlled smoke evacuation systems, and minimizing energy device usage are recommended.

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INTRODUCTION

The COVID-19 pandemic has been impacting our planet in an unprecedented way. Health care systems in several countries have collapsed in the face of a highly transmissible virus, potentially lethal and still poorly understood in its pathophysiology. Since the first cases of the disease caused by SARS-CoV-2, in the beginning of December 2019, not only medical practice has changed, but also the bases of social interaction, professional activity and the global economy have been hit hard.

In Urology, as in other specialties, surgeries have been reduced basically to emergencies. Elective surgeries for benign pathologies have been summarily postponed and elective oncological surgeries have been recommended in selected

cases of pathologies with greater aggressiveness such as radical cystectomy for muscle-invasive or very high-risk non muscle-invasive bladder cancer; retroperitoneal lymph node dissection for testicular cancer; radical nephrectomy for cT3 tumors; nephroureterectomy for upper tract urothelial cancers; radical orchiectomy for testicular cancer and adrenalectomy for specific aggressive adrenal cancer pathology. Radical prostatectomy for high-risk prostate cancer and partial nephrectomy for ≥ cT1b renal tumors should be performed in centers located in areas not severely hit by the pandemic where the resources available are sufficient (1, 2).

COVID-19 pandemic has therefore, affected and will continue to influence how surgeons will approach the patient care peri-operatively. A risk-benefit assessment of each patient undergoing surgery should be performed based on the urgency of the surgery and the risk of viral illness and transmission. Among surgeons worldwide, a concern with the use of minimally invasive techniques (laparoscopic and robotic) has been raised due to a proposed risk of viral transmission of the COVID-19 with the creation of pneumoperitoneum.

Our understanding of the process of viral transmission in surgery is limited. The virus responsible for COVID-19 (SARSCoV-2) belongs to the subgroup of coronaviruses that include the severe acute respiratory syndrome coronavirus (SARSCoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). Although very similar to these viruses, COVID-19 appears to be highly contagious due to its longer latency period. The only current known modality of transmission of the COVID-19 virus is through respiratory droplet transmission (3-5).

The mechanism for successful transmission is thought to be two-fold: human to human when the infected person coughs or exhales droplets that reach the other persons nose, mouth, or eyes to enter their respiratory tract; or contaminated surfaces when larger droplets produced from the infected person are spread onto surrounding surfaces and another person touches these contaminated surfaces and then touches their eyes, nose, or mouth.

Another proposed mechanism has been suggested, although sufficient evidence is lacking, that an aerosolizing procedure on an infected person creates smaller droplets from the respiratory tract that are thought to be able to reach up to 1-m distance reaching another person's nose, mouth, or eyes.

However, since the only proven mode of transmission of COVID-19 is through respiratory droplets, the risk of transmission from the abdomen is unclear (6).

Considering the hypothesis of a potential risk of exposure of the surgical staff to particles that could transmit COVID-19, during laparoscopic and robotic surgery, we reviewed the literature to evaluate the safety of these minimally invasive techniques during the global pandemic COVID-19.

Evidence

In pure laparoscopic or robotic assisted surgery, part of the technique is the establishment and maintenance of an artificial pneumoperitoneum; with this comes the risk of aerosol exposure for the operating room team. Electrosurgical devices, including electrocautery and vessel-sealing tools, are now widely used intraoperatively for hemostasis. These devices enable surgeons to perform minimally invasive surgery, however, the surgical smoke that arises from electrosurgical devices may expose the surgical team to potentially harmful chemicals, viruses and viable cells (7-11). Therefore, acquiring an infectious disease from surgical smoke represents a potential health hazard.

Ultrasonic scalpels or electrical equipment commonly used in laparoscopic surgery can produce large amounts of surgical smoke, and in particular, the low-temperature aerosol from ultrasonic scalpels cannot effectively deactivate the cellular components of virus in patients. Li et al., found that after using electrical or ultrasonic equipment for 10 minutes, the particle concentration of the smoke in laparoscopic surgery was significantly higher than that in traditional open surgery (12). The reason may be that due to the low gas mobility in the pneumoperitoneum, the aerosol formed during the operation tends to concentrate in the abdominal cavity. Sudden release of trocar

valves, non-air-tight exchange of instruments, or even small abdominal extraction incisions can potentially expose the health care team to the pneumoperitoneum aerosol.

Zhang et al. demonstrated the high prevalence of SARS-CoV-2 in stools (2, 13), but also the suggestion that the virus can be found in the gastrointestinal mucosa. Thus, despite the lack of evidence to demonstrate or refute the viral transmissibility from the gastrointestinal tract, a threat that the virus can be transmitted from the abdomen exists. And some have theorized that the environment created by pneumoperitoneum for laparoscopy creates a relatively stagnant heated volume of gas in the abdominal cavity which may subsequently allow for a concentrated aerosolization of the virus. Thus, it is hypothesized that sudden bursts of this pneumoperitoneum from trocar valves during exchange of instruments or during the venting of trocars can allow for transmission of the virus (6).

Many studies have reported the presence of other viruses in surgical smoke. Kwak et al., presented the first report of hepatitis B virus isolated from laparoscopic surgical smoke, successfully detected using a high efficiency collector and nested PCR, and higher concentration of surgical smoke particles in laparoscopic compared to open surgery (1, 13-15). Zheng et al. postulated a potential risk of SARS-CoV-2 diffusion during all minimally invasive procedures with possible subsequent infection of medical personnel working in operating rooms (15).

Although it is feasible for aerosols and microparticles to be released into the operating room during minimally invasive surgery, there is no scientific evidence so far, that particularly in the case of COVID-19, could demonstrate a greater risk of contamination of the surgical team by this route, and, to date, there are no reports of contamination of the surgical team by the coronavirus during minimally invasive surgery.

In fact, pure laparoscopic surgery, or robot assisted, seems to be safer, favoring both patients and the professional team that assists them. Although the risk of exposure to aerosols appears to be higher in minimally invasive surgery than in open surgery, the latter has an extremely higher risk of spreading micro and macroparticles, blood and tissues to the surgical team.

Actually, the use of laparoscopy during this pandemic can contribute to decreased length of stay as compared with open surgery as well as minimizing the need for medical treatments, and in turn increasing availability of beds, a limited resource. Laparoscopy is less traumatic compared with a laparotomy, and in the case of a patient infected with COVID-19, a minimally invasive operation as compared with an open procedure might result in improved survival and faster recovery. Laparoscopy allows for a self-contained operative field with less and possibly no spillage of fluids and tissues, thus decreasing any risk to the operative staff. For this reason, in the 1990s during the acquired immunodeficiency syndrome (AIDS) epidemic, laparoscopic surgery was strongly encouraged over open surgery in patients infected with the human immunodeficiency virus (HIV) (16, 17).

Finally, laparoscopic surgery, and in particular robotic surgery, allow for the staff and surgeon to be remote from the patient and from each other minimizing the risk of transmission of virus not only from the patient to the staff but also from operative staff infecting each other, as operative staff are in much closer proximity to each other and to the patient during open operations. Thus, as reviewed here, the benefits of laparoscopy that we have promoted and valued for many years can still provide a benefit even during the current pandemic and may even offer other benefits to this specific situation we may not have otherwise appreciated (6).

Few studies have been performed on viral transmission during surgery, but to date there is no study that demonstrates or can suggest the ability for a virus to be transmitted during surgical treatment whether open or laparoscopic. There is no consensus, among societies, on limiting or restricting laparoscopic or robotic surgery; however, there is expert consensus on the modification of standard practices to minimize any risk of transmission (6).

CONCLUSIONS

Considering the data available so far, laparoscopic or robotic surgery can be considered safe procedures and should be performed, observing

some modifications in order to reduce any possible risk to the surgical team. Despite very little evidence to support viral transmission through minimally invasive surgery, it is common sense to adopt measures that minimize any risk making modifications to surgical practice such as the use of smoke evacuation, lowering the pneumoperitoneum as low as possible and minimizing energy device usage among other measures to minimize operative staff exposure to aerosolized particles (Table 1 and 2) (11). Avoid intraoperative smoke formation by lowering electro cautery power settings, using bipolar electro cautery, using electro cautery or ultrasonic scalpels parsimoniously. More extensive use of sutures and clips in the operating room is recommended. Special attention must be paid when removing trocars at the end of a procedure, using suction to remove smoke and aerosol. Limit the smoke dispersal or spillage from trocars by lowering the pneumoperitoneum pressure. Usage of pressure-barrier insufflator systems that maintain a forced-gas pressure barrier at the proximal end of the trocar might be of benefit (2).

Table 1 - Expected debris from the various categories of energy devices used in the abdomen.

Surgical Device	Plume
Ultrasonic Scalpel	0.35 – 6.5 microns
Laser ablation	0.3 microns
Electro cautery	< 0.1 microns

Finally, the need of appropriate personal protective equipment (PPE) should be reinforced. Nasopharyngeal samples should be obtained and tested (PCR) for all patients undergoing surgical procedures. Only negative COVID patients should undergo surgery. Positive COVID patients should be deferred until the patient has recovered from the disease and has tested negative. Positive COVID patients, under emergency scenarios, should be treated as much as possible in a conservative approach and only taken to surgery if the case is life threatening, since the mortality rate in these cases is as high as 20% (18).

RECOMMENDATIONS

Prevention and management of aerosol dispersal:

- During operations, instruments should be kept clean of blood and other body fluids. Special attention should be paid to the establishment of pneumoperitoneum, hemostasis, and cleaning at trocar sites or incisions to prevent any gush of body fluid caused by air leakage or uncontained laparotomy incisions.
- Once ports are placed, they should not be vented if possible.
- The insufflator should be "on" before the new port valve is opened to prevent gas from back flowing into the insufflator.
- Liberal use of suction devices to remove smoke and aerosol during ope-

Table 2 - Filtration devices for laparoscopy and robotics.

Device	Filter (microns)	Efficiency (%)
N95	0.3	95
HEPA	0.3	99.7
ULPA	0.05	99.9
ConMed PlumePort ActiV	0.1	99.9
Stryker PureView Active Plume	0.1	99.9
Stryker Pneumoclear Insufflator	0.051	99.9
ConMed AirSeal System	0.01	99.9

rations, and especially, before converting from laparoscopy to open surgery or any extra-peritoneal maneuver.

- Avoid using 2-way pneumoperitoneum insufflators to prevent pathogens colonization of circulating aerosol in pneumoperitoneum circuit or the insufflator. It's recommended using a closed circuit with smoke evacuation device with high--efficiency particle air (HEPA) or ultra--low particulate air (ULPA) filters or best available equivalent substitute (6, 15). (Table-2 and Figures 1A-C)
- All pneumoperitoneum should be safely evacuated from the port attached to the filtration device before closure or trocar removal, specimen extraction, or conversion to open.
- Suture closure devices that allow for leakage of insufflation should be avoided. The fascia should be closed after desufflation.

Management of artificial pneumoperitoneum:

- Keep intraoperative pneumoperitoneum pressure and CO2 ventilation at the lowest possible levels, since many emergency and non-emergency cases can be performed with an insufflation pressure of 12 mmHg or lower.
- Reduce the Trendelenburg position time as much as possible (2, 6, 15).
- At the conclusion of the operation to desufflate the abdomen use a smoke evacuation device or suction substitute (6).

Operation techniques:

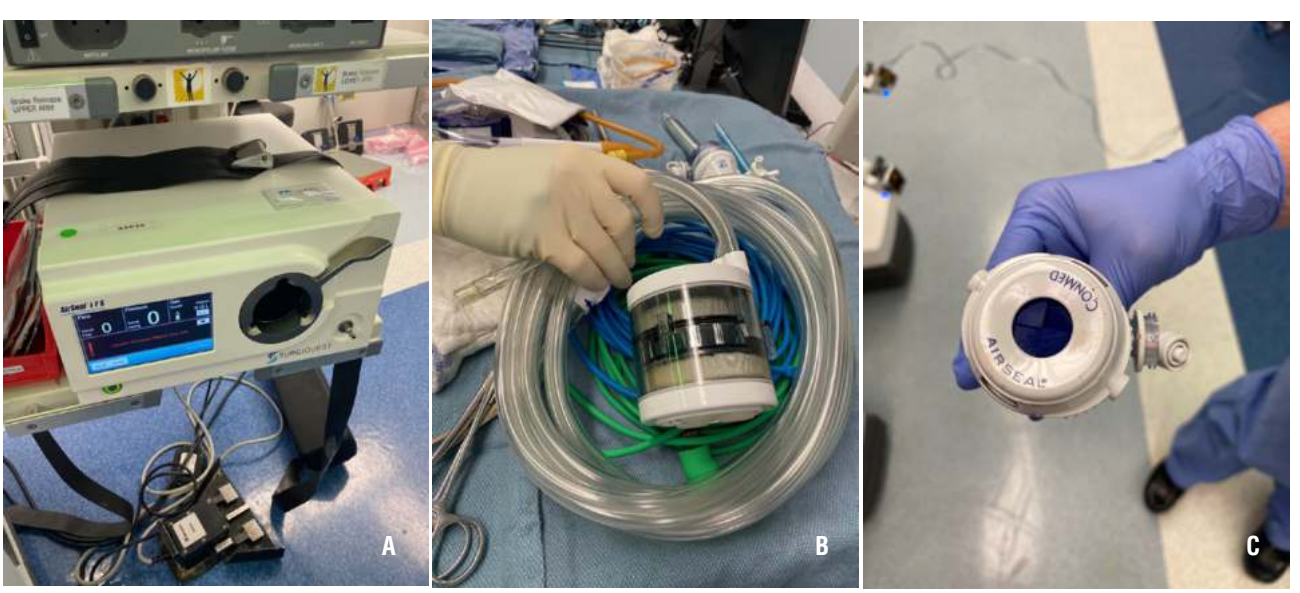
- Minimize the use of energy devices during procedures when possible. When energy is needed, avoid the ultrasonic scalpel and lower energy settings to minimize surgical smoke (6, 15).

Surgery should be performed by an experienced laparoscopic or robotic surgeon to minimize length of surgical time as much as possible.

Modifications for Robotic Surgery:

- Use the same insufflators and smoke evacuation systems. Additional precautions to take with robotic surgery to avoid leakage from trocars include:

Figures - 1A, B, and C: Conmed® Airseal System.



(1A: Insufflator; 1B Filter and tubing; 1C Special Conmed® Trocar)

- Always using the trocar reducers in 12-mm trocars when inserting 8-mm or 5-mm instruments through the 12-mm trocars. Since the robotic ports and reducers are 8 mm, there is still potential leakage of pneumoperitoneum with 5-mm instruments. Thus, the use of laparoscopic 5-mm instruments through even the 8-mm trocars should perhaps be minimized if possible (6).
- Clean the console and the eyepiece, before and after using the system.

Operating staff protection:

- Best efforts must be made to raise awareness of the occupation protection on operating staffs, including surgeons, anesthetists, nurses and all possible transiting persons in the OR.
- Correct 2-way protective apparel (goggles, visor, mask, and body protective garb) should be routine.
- When engaging a suspected or diagnosed patient, tertiary dress code should be applied according to the protocols which also include strengthening OR ventilation and installing air purification equipment (2, 6, 15).

CONFLICT OF INTEREST

None declared.

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