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Covid-19: Why the Kidney Care is so much Affected?

In December 2019, a series of cases of pneumonia of unknown origin were reported in Wuhan, the capital city of Hubei province in China. The causative virus was isolated and characterized in January 2020.[1] On January 12, 2020, the World Health Organization (WHO) named the virus as the 2019 novel coronavirus (2019-nCoV). On January 30, 2020, the WHO issued a public health emergency of international concern (PHEIC) and on February 11, 2020, the WHO formally named the disease caused by the novel coronavirus as coronavirus disease 2019 (COVID-19). The International Committee on Taxonomy of Viruses classified and renamed 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 11, 2020, the WHO labelled the global spread of COVID-19 as a pandemic.

Though to start with the COVID-19 primarily had respiratory symptoms as presenting features, soon it was realized that it is a systemic disease involving other organs of the body also like heart, nervous system, liver, blood vessels and kidney. Later it became clear that some of the patients may present with non-respiratory symptoms. Host susceptibility, particularly elderly and peoples with underlying diseases, hypertension, cardiac diseases, bronchial asthma, diabetes, chronic kidney disease (CKD) etc., influence the risk of acquiring and progression of COVID-19.

There are three issues related to kidney diseases and COVID-19.

Firstly, pre-existing kidney diseases, including hypertension, CKD, a glomerular disease requiring immunosuppressive therapy, the patients on dialysis, and with kidney transplants are all immunocompromised patients and risk of getting COVID-19 is not only more but also clinical manifestation may be atypical. Also, the primary aetiology of CKD being diabetes and hypertension make these patients at further risk of severe COVID-19 and poorer outcome.

Secondly, SARS-CoV-2 can also affect the kidney. The mechanism of kidney injury by COVID-19 appears multifactorial, although precisely, remains unknown.[2] The direct viral cytopathic effect on kidney tissue is a postulated mechanism, which is supported by the finding of viral nucleic acid material of CoV in blood and urine in SARS-CoV as well as the patients with COVID-19.[3] The direct effector T-cell-mediated injury and the immune complex-mediated glomerular injury with viral antigen and specific antibody could be another plausible mechanism. The other mechanism could be by inducing sepsis and the cytokine storm theory.[4] The cytokines and other mediators are released after COVID-19 infection leading to sustained inflammatory response leading to hypotension, hypoxia, shock, and target organ injuries. The incidence of AKI with COVID infection reportedly varies from 3% to 9%. A larger prospective study reported the overall incidence of 5.1%,[5] Li et al.[6] found that 34% of the patients had albuminuria on the first day of admission, and 63% developed proteinuria during the hospital stay.

Thirdly, due to various measures taken by local government and policymakers regarding containment of COVID-19, providing kidney care to patients became a significant issue. Lockdown had resulted in getting life-saving medicines for CKD, glomerular disease and kidney transplant. Elective surgeries, including elective living-related renal transplant and also elective CAPD catheter insertion, were practically cancelled across the country by the government policy to divert human resources and other facilities in COVID-19 care. Deceased donor transplant, though considered an emergency procedure had also come to halt. Providing haemodialysis became a challenge. Pre-dialysis testing for COVID-19, dialysing in the isolation room, preventing COVID-19 among dialysis patients and staff and non-availability of dialysis consumables, all became challenges and controversies. Panic resulting in the closing of some of the dialysis units temporarily had further increased the problems.

With such a scenario in the country, the Indian Society of Nephrology constituted a COVID-19 Task Force* to address these issues to guide the colleagues in the best way to handle the situation of patients of kidney disease while balancing the ground realities and government policies. Country’s leading nephrologists were put on board to write on different issues related to caring of patients of various kidney diseases and those manuscripts have been put in the symposium in the current issue.

We hope that these documents will be useful to the colleagues for better management of the situation and patient care.

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Epidemiology, Genomic Structure, the Molecular Mechanism of Injury, Diagnosis and Clinical Manifestations of Coronavirus Infection: An Overview

Abstract
COVID-19 is caused by a novel beta coronavirus (SARS-CoV-2) strain that was first discovered in 2019 in the Wuhan city of China. Based on virus genome sequencing studies, the bat is suspected as the natural host of virus, and infection might be transmitted from bats via unknown intermediate hosts like reptiles and snakes etc., to infect humans. COVID-19 is transmitted from person to person contact, primarily via droplet infection within the incubation period or after clinical manifestations of fever, cough, sneezing, sputum, dyspnea, and pneumonia and through contaminated fomites. COVID-19 enters the respiratory tract through the ACE2 receptor on alveoli through binding of s-protein of the virus and causes injuries though the cytopathic effect, as well as cytokines and other mediators, released after developing sepsis. ACE 2 is almost 100-fold higher in kidneys than lung, and the virus can also involve the kidney in the same manner. Kidney involvement manifests in the form of proteinuria, hematuria, and an acute rise in serum creatinine. Kidney involvement is an independent risk factor for mortality. Diagnosis is primarily made by detecting viral RNA by reverse transcriptase polymerase chain reaction (rtPCR) in nasopharyngeal swab samples. Role of antibodies, both IgM and IgG are still evolving and at best restricted for epidemiological purpose. Though a large number of treatments, including hydroxychloroquine, anti-viral, convalescent plasma etc., are being tried, as of now treatment is symptomatic only.

Keywords: Acute kidney injury, COVID-19, coronavirus, epidemiology, mechanisms, sepsis, severe acute respiratory syndrome

Introduction
Coronaviruses (CoV) are amongst the newly emerging zoonotic virus which is transmitted between animals and human beings. In the past, it has caused illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). The SARS-CoV was transmitted from civet cats to humans and MERS from dromedary camels to humans. Many other coronaviruses are still circulating in animals that are not found in humans to date.

Corona Virus Disease-19 (COVID-19) is a novel CoV induced disease that was first discovered in December 2019, which was not previously reported in humans. This CoV was renamed several times after discovery, first of all, as a newly identified β-coronavirus in Wuhan. On 12th January 2020, the World Health Organization (WHO) renamed it as the 2019-novel coronavirus (2019-nCoV), and subsequently on 11th February 2020, the Coronavirus Study Group of the International Committee on Taxonomy of viruses of WHO proposed the name SARS-CoV-2 for this virus, and the disease caused by the virus was called COVID-19.

Global Situations of COVID-19
At the end of 2019, SARS-CoV-2 caused a cluster of pneumonia cases in Wuhan, a Chinese city, in the Hubei province of China. On 30th January, the outbreak was declared as Public Health Emergency of International Concern (PHEIC) and later a declared global pandemic by WHO. The disease gradually gripped the entire world. The epicenter of pandemic later changed from Wuhan city in China to Europe and the USA.
As on 21st March 2020, WHO reports, there were 266,073 confirmed cases, and 11,184 confirmed deaths in 183 countries. On 22nd April, WHO reported region-wise situation of COVID cases and death, globally 2,471,136 confirmed and 169,006 deaths. And region wise; the European Region 1219,486 cases and 109,952 deaths; Americas 925,291 cases and 44,775 deaths; the Eastern Mediterranean Region 139,349 cases and 6326 deaths; Western Pacific Region 136,271 cases and 5793 deaths; the South-East Asia Region 33,912 cases and 1427 deaths; and African Region 16,115 cases and 720 deaths. WHO reported a very high level of risk assessment. The global pandemic indicates that the entire world is affected by this COVID pandemic [Figure 1].

India-specific situation

India noticed the first case of the COVID pandemic on 30th January 2020. On March 23, the Indian Council of Medical Research (ICMR) data revealed a result of a total of 18,383 samples tested from 17,493 individuals; 415 were positive, and there were 7 deaths due to COVID-19. The Center for Disease Dynamics, Economics and Policy (CDDEP), applying mathematical models used in the USA, pointed out that possibly 300 million (30 crore) cases will occur in India, out of them 10 crores will face severe COVID infection. Looking at the incidence of 5.1% of AKI in severe cases, there would be 5.1 million AKI patients because of SARS-CoV-2, and presumably many of them may require renal replacement therapy (RRT). It is estimated that with community spread COVID-19 in India with limited resources and health infrastructure, it could be challenging to combat the situation of patients with multiorgan failure and kidney failure, if the disease spreads fast within 2-3 months.

Lockdown effect in India

To curb the transmission of the virus in the community, India observed a 14-hour voluntary public curfew on 22 March 2020, and subsequently, on 24th March, a nationwide lockdown for 21 days was implemented, affecting the entire 1.3 billion population of India. On 14th April, the lockdown was extended till 3 May and further till 17th May, with the lifting of restriction as per the zones defined on number of new cases seen in the different areas.

The lockdown has reduced the rate of positivity from 16% on 14th April 2020 to 6% on 28th April 2020; and the death rate also declined from 9% to 6% during the same period. Till date, India successfully prevented widespread community spread. As of 28th April 2020, the Ministry of Health and Family Welfare has confirmed a total of 29,974 cases, 7,027 recoveries (including 1 migration), and 937 deaths in the country. The COVID-19 affected almost all states of India, which has been highlighted in Figure 2. Experts suggest that the number of infections could be much higher as India’s testing rates are among the lowest in the world. The infection rate of COVID-19 in India is reported to be 1.7, significantly lower than in the worst affected countries. Despite lower testing rates, the case fatality rate in India and other south Asian countries appears low because of several reasons, few being the early implementation of lockdown; and the universal BCG vaccination in childhood, which induces non-specific protection mediated via the induction of innate immune memory. The hot and humid environment may be another factor as high COVID pandemic related fatality observed in latitude band with average temperature below 17degree Celsius and a Chinese study showed both one unit increase of temperature and absolute humidity were associated with the decreased COVID-19 death. The individual host immunity and virulence factor may also affect the fatality. Possibly the lower virulence of the COVID strain and proportionately lower elderly population than the western world in India and other parts of South Asia may be a plausible explanation of low

Figure 1: Global map showing entire world is affected with COVID pandemic. (source https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/world-map.html)
The droplets do not travel more than 6 feet and do not linger in the air also. The aerosol spread is uncommon; however, the aerosol-generating procedures like intubation, suction, nebulization, etc., may transmit the disease. However, a report revealed that SARS-CoV-2 might remain viable in aerosols under experimental conditions for at least three hours. The possibility of transmission is higher in the early phase as soon as symptoms appear as the viral RNA peaks during that period. However, it may transmit during the incubation period as well. The incubation period is typically within two weeks of exposure, with the majority occurring within 4-5 days of exposure.

According to a joint WHO-China report, the rate of secondary COVID-19 ranged from 1-5% among tens of thousands of close contacts of confirmed patients in China. In the United States, the symptomatic secondary attack rate was 0.45% among 445 close contacts of 10 established patients. SARS-CoV-2 has been detected in non-respiratory specimens, including stool, blood, and ocular secretions, but the role of these sites in the transmission is uncertain. Live viruses had also been cultured from stool; however, the fecal-oral transmission did not appear to be a significant factor in the spread of infection.

**Period of infectivity**

The period of infectivity is uncertain in COVID-19. The detection of viral RNA from the respiratory tract does not always indicate the presence of an infectious virus. The patient might be more infectious during the earlier stage of infections. The viral RNA from the upper respiratory tract specimen after the onset of symptoms is usually higher than the later phase of the disease. Additionally, in a study of nine patients with mild COVID-19, infectious virus was isolated from nasal/oropharyngeal and sputum specimens during the first week of illness, but not after this interval, despite continued viral RNA levels at these sites. A modeling study from China showed that infectiousness started 2.3 days before symptom onset, peaked 0.7 days before symptom onset and declined within seven days, particularly after isolation of these patients.

However, an asymptomatic individuals may also transmit the disease during the incubation period. A Singapore study in an analysis of 157 locally acquired COVID-19 showed the transmission rate of 6.4% during the incubation period. The exposures occurred one to three days before symptoms in these patients. The exact estimation of asymptomatic infection will be possible with serologic testing, which is still in the phase of testing and validation.

The duration of viral shedding varies with degree of severity. With milder illness, 90% showed negative test by ten days, while severe illness shows a more prolonged period of positivity. However, another study has shown more prolonged shedding of the virus of a median duration.

**Epidemiology**

The impact of a pandemic depends on the number of infected persons, transmissibility, and the clinical severity of the infection. The world needs to expand public health activities, social and economic planning in reference to the SARS-CoV-2, and reduced the impact on public health, social and economic well-being of the people. Till March end, the epidemiology of COVID-19 was not very clear. Now, with increasing information on the epidemiology of COVID-19, the newly affected parts, including India, evolved with the concept of lockdown and reduced the transmission as an effective way to curb the transmission.

**Mode of transmission**

Epidemiological studies in Wuhan at the beginning of the outbreak identified an initial association with a seafood market that sold live animals for food purposes, where most of the early patients had worked or at least visited there. The market was traced as the source, and subsequently, the market was closed for disinfection. However, as the outbreak progressed, person-to-person spread became the primary mode of transmission.

The respiratory droplets released during cough, sneezing, talks, and mucus secretion are the dominant medium of transmission. The infection occurs if a person inhales such droplets or touches the contaminated surface with droplets and, subsequently, their own eyes, nose, and mouth. The respiratory droplets released during cough, sneezing, talks, and mucus secretion are the dominant medium of transmission. The infection occurs if a person inhales such droplets or touches the contaminated surface with droplets and, subsequently, their own eyes, nose, and mouth.

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**Figure 2: Map of the 2019-nCoV outbreak in India as of 28 April 2020, 17:00 Hrs. 5000+ confirmed cases 1000–4999 confirmed cases 500–999 confirmed cases 100–499 confirmed cases 50–99 confirmed cases 1–49 confirmed cases shifted to another state (Source https://en.wikipedia.org/wiki/2020_corona_virus_pandemic_in_India accessed on 28th April 2020)**

fatality. However, these factors need to be confirmed in a scientific study.
of 24 days. However, detection of viral RNA in sample does not correlate with infectivity. In the study of nine patients with mild COVID-19, the infectious virus was not detected from respiratory specimens when the viral RNA level was <10^6 copies/mL.\cite{39}

**Environmental contamination**

Environmental contamination and fomite transmission from a contaminated surface to mucous membranes of the nose, eye, mouth etc., is possible in heavy viral contamination settings. A Singapore study showed the presence of viral RNA on handles, light switches, bed and handrails, interior doors and windows, toilet bowl and also the sink basin in the airborne infection isolation room of a patient with symptomatic mild COVID-19.\cite{28} However, routine cleaning with sodium dichloroisocyanurate cleared the virus from these surfaces. SARS-CoV-2 may persist for differing time interval on different surfaces. The various disinfectants including ethanol at concentrations between 62 and 71% inactivate SARS-CoV-2 within one minute.\cite{43} The duration of viral persistence on surfaces depends on type of surface, the ambient temperature, relative humidity, and the size of the initial inoculum.\cite{44,45}

**Risk of animal contact**

Despite the thought of initial transmission from animals to human beings, there is no evidence to suggest domestic animals are a major source of infection in humans for SARS-CoV-2. There have been no reports of domesticated animals transmitting SARS-CoV-2 infection to humans. Experimental studies showed the virus replicated in cats after intranasal inoculation, but not in dogs.\cite{46} CDC recommends that pets should be kept away from other animals or people outside of the household. People with confirmed or suspected COVID-19 try to avoid close contact with household pets, in similar fashion as with other human household members for the duration of their quarantine period.\cite{47}

**Protective Immunity and risk of reinfection**

The definitive evidence of the development of protective antibody in infected COVID patients is still emerging.\cite{38,39} The presence of neutralizing activity in convalescent plasma has been reported.\cite{40} In a study on 23 recovered COVID-19 patients revealed, antibodies to the receptor-binding domain of the spike protein and the nucleocapsid protein appears by day 14 following onset of symptoms. The study also showed that antibody titers by enzyme-linked immunosorbent assay (ELISA) correlated with neutralizing activity.\cite{41} Having neutralising activities, these antibodies are likely to be protective. The US-FDA has granted emergency use authorization for tests that qualitatively identify antibodies against SARS-CoV-2 in serum or plasma.\cite{49} The serologic screening will be an important tool to understand population immunity and distinguishing peoples at lower risk for reinfection.

**Risk factors**

Older age, diabetes mellitus, chronic lung disease, cardiovascular disease, obesity, immunocompromised states, chronic kidney disease and liver diseases are the risk factor for the COVID-19. All ages and both sexes are are affected. Middle-aged adults and elderly above 60 years are most commonly affected with predominantly severe disease and increased mortality.\cite{50-52} The US-CDC advocated that the people with the immunocompromised state, severe obesity, and liver disease are at a risk for severe illness.\cite{53} Males had disproportionately high number of deaths in cohorts from China, Italy and the United States.\cite{16,35,52} The pre-existing comorbidities are associated with a higher mortality.

**Structure and viral genome of coronavirus in brief**

The SARS-CoV-2 is a β-coronavirus, which is enveloped non-segmented positive-sense RNA virus of subfamily Orthocoronavirinae of the Coronaviridae family.\cite{11,54} CoVs are divided into four genera called alpha (α), beta (β), gamma (γ) and delta (δ) CoV. α- and β-CoV can infect mammals, while γ- and δ-CoV tend to affect birds. Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats.\cite{54,55} Six CoVs have been discovered which can affect human, among which α-CoVs HCoV-229E and HCoV-NL63, and β-CoVs HCoV-HKU1 and HCoV-OC43 had low pathogenicity, and cause common cold like milder respiratory symptoms. The other two known β-CoVs, SARS-CoV, and MERS-CoV lead to severe and fatal respiratory tract infections.\cite{2,54} SARS-CoV-2 is 29.9 kb.\cite{55} While SARS-CoV and MERS-CoV have positive-sense RNA genomes of 27.9 kb and 30.1 kb, respectively.\cite{56} It has been shown that the genome of CoVs contains a variable number (6-11) of open reading frames (ORFs).\cite{57}

Figure 3 depicts the structure of the CoVs. CoVs are round or elliptic and often pleomorphic form, with a diameter of approximately 60–140 nm. The single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 proteins.
amino acids. Two-thirds of viral RNA, mainly located in the first open reading frame (ORF 1a/b), encodes 16 non-structure proteins (NSPs). The rest part of the virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and also several accessory proteins that interfere with host immune response.[55,58] The primary functions that direct coronavirus RNA synthesis and processing reside in nonstructural protein (nsp) 7 to 16, which are cleavage products of two large replicase polyproteins translated from the coronavirus genome.[59-61]

The sequencing studies of Wu et al.[60] revealed genomic and phylogenetic similarity of the SARS-CoV-2 with SARS-CoV, particularly in the S-protein gene and the receptor binding domain (RBD). This indicated the capability of direct human transmission like SARS-CoV. The whole-genome sequence studies showed that COVID-19 appears closer to the SARS-like bat CoVs as compared to the known SARS-CoV and MERS-CoV. Chan et al. have proven that the genome of the new HCoV, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 89% nucleotide identity with bat SARS-like-CoVXC21 and 82% with that of human SARS-CoV.[64] For this reason, the new virus was called SARS-CoV-2.[199] The majority of genomically encoded proteins of SARS-CoV-2 and SARS-CoVs were similar, except few differences in some amino acid substitutions in NSP2, NSP3, spike protein and receptor binding domains.[60,61]

Another recent research suggested[61] that the mutation in NSP2 and NSP3 play a role in infectious capability and differentiation mechanism of COVID-19. A study by Zhang et al.[62] revealed that SARS-CoV-2 was mutating in different patients in China. Tang et al.[63] conducted a population genetic analysis of 103 COVID-19 genomes and classified out two prevalent types of COVID, L type (approximately 70%) and S type (approximately 30%). The strains in L type, derived from S type, are evolutionarily more aggressive and contagious. There is a need to keep an eye over this novel CoVs for their virulence and epidemic spread over the globe, at present.

It was also found that the genome sequence of SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13, whereas it shares 79.5% identity to SARS-CoV. Based on virus genome sequencing results and evolutionary analysis, the bat is suspected as the natural host of virus origin, and COVID-19 might be transmitted from bats via unknown intermediate hosts like pangolins, other reptiles, and snakes etc., to infect humans.

Overall molecular mechanism of injury by COVID-19 (SARS-CoV-2)

S-protein of SARS-CoV-2 binds to host cell receptors, angiotensin-converting enzyme 2 (ACE2), which is a critical step for virus entry into cell.[64] ACE2 is cell receptor for COVID-19 and regulates the transmission across the species and between human beings as well.[65-66] S-protein contain two subunits, S1 and S2.[67-69] S1 determines the virus-host interaction and cellular tropism with the vital function domain-RBD, while S2 mediates virus-cell membrane fusion by two tandem domains, heptad repeats 1 (HR1) and HR2.[66-68]

S-protein and ACE2 binding efficiency of COVID-19 is 10- to 20-fold higher than that of SARS-CoV.[70] For SARS-CoV, the cleavage of trimer S protein is triggered by the cell surface-associated transmembrane protease serine 2 (TMPRSS2)[71] and cathepsin,[72] however, the possible molecules facilitated membrane invagination for SARS-CoV-2 endocytosis are still under investigations.

After membrane fusion, the viral genome RNA is released into the cytoplasm, and the uncoated RNA translates two polyproteins, pp1a and pp1ab,[73] which encode non-structural proteins, and form replication-transcription complex (RTC) in double-membrane vesicle.[74] Continuously RTC replicates and synthesizes a nested set of subgenomic RNAs,[73] which encode accessory proteins and structural proteins. Mediating endoplasmic reticulum (ER) and Golgi bodies,[76] newly formed genomic RNA, nucleocapsid proteins, and envelope glycoproteins assemble and form viral particle buds. Lastly, the virion-containing vesicles fuse with the plasma membrane to release the virus leading to viremia.

The S2 subunit of Covid-19 containing a fusion peptide, a transmembrane domain, and cytoplasmic domain is highly conserved, which could be a target for antiviral targeting against S-2 (anti-S2) compounds. The spike RBD presents only a 40% amino acid identity with other SARS-CoVs. The ORF3b has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally different from those of SARS-CoV, may be an area of interest and research in the future.[77]

Mechanisms of kidney and other organ injuries

Host susceptibility, particularly elderly and peoples with underlying diseases, hypertension, cardiac diseases, bronchial asthma, diabetes, chronic kidney disease etc., influence the risk of acquiring and progression of COVID-19. The mechanism of kidney injury by COVID-19 appears multifactorial and, although precisely, remains unknown.[77] The direct viral cytopathic effect on kidney tissue is a postulated mechanism, which is supported by the finding of viral nucleic acid material of CoV in blood and urine in SARS-CoV as well as COVID-19 patients.[17,78] The molecular study showed CoV uses ACE2 receptor for cell entry. ACE2 expression is 100-fold higher in kidney tissues than the lung.[50] It makes sense to postulate that ACE2 dependent pathway may be used by CoV to infect kidneys more severely than the lung. However, clinical
observation is different from more lung involvement than the kidney.

The direct effector T cell-mediated injury and the immune complex-mediated glomerular injury with viral antigen and specific antibody could be another plausible mechanism. However, the present evidence of information with normal glomerular aspect on microscopy and absence of electron-dense deposit in SARS-CoV patients do not support this hypothesis. Furthermore, there is report of collapsing glomerulonephritis in COVID-19 and proteinuria and hematuria in significant number of patients.

The other mechanism could be by inducing sepsis and the cytokine storm theory. The cytokines and other mediators are released after CoV infection leading to sustained inflammatory response leading to hypotension, hypoxia, shock, and target organ injuries. The clinical pictures of patients with COVID-19 with sepsis support this hypothesis. The manifestations are particularly severe, with a wide range of signs and symptoms of multiorgan involvement. These signs and symptoms include respiratory events such as severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs expressed as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia. However, these findings suggest the probable mechanism of AKI in many terminal cases. Wang et al. showed that 138 patients with COVID-19 disease, who were admitted in ICU, showed a tendency towards increased creatine kinase levels. It contributes to AKI indirectly through the effects on renal tissues, because of hypotension, hypoxia, shock, and rhabdomyolysis.

Clinical manifestations

There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. Pneumonia appears to be the most severe and frequent manifestation of infection, characterized primarily by fever, cough, dyspnea and bilateral lung infiltrates on chest imaging. In a study describing 138 patients with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of illness were fever (99%), fatigue (70%), dry cough (59%), anorexia (40%), myalgias (35%), dyspnea (31%) and sputum production (27%).

However, different clinical manifestations were noticed from other parts of the world. A study report from New York city of USA, one of the worst affected city in the world showed the median age of 62 years, predominantly males (61%), and obese (36%). The clinical symptoms were cough (79%) more common than China, fever (77%) relatively less than China, and dyspnea (57%). Gastrointestinal symptoms (diarrhea, 24%; nausea and vomiting, 19%) were relatively common. The US-CDC added a few new symptoms in COVID checker list with chills, repeated shaking with chills, muscle pain, headache, sore throat and new loss of taste or smell.

The mild disease is usually characterized by fever, malaise, cough, upper respiratory symptoms, in the absence of dyspnea. Most of these patients do not need hospitalization. The severe disease is characterized by hypoxia (oxygen saturation ≤93 and on room air or PaO2/FiO2 < 300 mmHg), tachypnea (respiratory rate >30 breaths per minute) or respiratory distress, more than 50% involvement of the lung parenchyma on chest imaging and other organ involvement.

Respiratory failure needing to ventilatory requirement also varied in different countries. Respiratory failure requiring mechanical ventilation occurred in a third of the patients in the USA, which was relatively greater than other parts of the world. 30% of the patients required mechanical ventilation (MV) before the requirement of supplemental oxygenation, which indicates that a substantial proportion deteriorates soon after the presentation. The patients needing MV were predominantly male (71% vs. 56%) and obese (43% vs. 32%). They had elevated liver function tests and other inflammatory markers. The other notable complications in those who required ventilatory support include need for vasopressor support (95%), cardiac arrhythmias (19%), bacteremia (12%), and new RRT (13%). Besides respiratory tract, the involvement of other organs such as the kidney, heart, digestive tract, blood, and nervous system also reported as for MERS. Kidney specific manifestations

Kidney involvement may be directly due to SARS-CoV-2 mediated injury or, a part of multiorgan dysfunction consequent upon cytokine storm. However, kidney involvement is a strong and independent predictor of mortality with COVID. The incidence of AKI with COVID infection reportedly vary from 3%–9%. A larger prospective study reported the overall incidence of 5.1%. Li et al. found that 34% of patients had albuminuria on the first day of admission and that 63% developed proteinuria during the hospital stay. 19% of the people showed an elevated level of plasma creatinine. Each one of those (27/27) who had computerized tomography (CT) scan showed radiographic abnormalities of the kidneys with reduced density suggesting inflammation and edema. The study also emphasized that renal impairment may be an independent factor of mortality. A prospective study showed that on admission, 43.9% of the patients had proteinuria, and 26.7% had haematuria. The prevalence of elevated serum creatinine and estimated glomerular filtration under 60 ml/min/1.73 m² were 14.4, and 13.1%, respectively. Cox proportional hazard regression confirmed that elevated baseline serum creatinine was an independent predictor of mortality. The hazard ratio also increases with the staging of AKI from 1.9 in stage-1, 3.51 in stage-2, and
Diagnosis

Reverse transcriptase polymerase chain reaction (RT-PCR)

The sample collection and storage for the diagnosis in a resource-limited place is also challenging. The WHO recommends collecting specimens from the upper respiratory tract (nasopharyngeal - and/or opharyngeal samples); and lower respiratory tract such as sputum, endotracheal aspirate, or bronchoalveolar lavage (BAL). The collection of BAL samples should only be performed in patients on MV. The samples require storage at four degrees celsius. Lower tract samples may have greater sensitivity than upper respiratory tract specimens.

A study showed that pharyngeal virus shedding was very high during the first week of symptoms with a peak on day 4 and was readily isolated from the throat- and lung-derived samples. However, it was not isolated from stool samples despite high virus RNA concentration. Blood and urine never yielded a virus. Viral replicative RNA intermediates confirmed active replication in throat samples. Independent replication of sequence -distinct virus was also observed in throat and lung samples from the same patient. The shedding of viral RNA from sputum outlasted the end of symptoms. Seroconversion occurred after seven days in 50% of patients and in majority of patients by day 14. However, this event was not universally followed by a rapid decline in viral load.

In the laboratory, a reverse transcriptase polymerase chain reaction (RT-PCR) is used for the amplification of the genetic material extracted from the saliva, mucus, and other samples. It involves the synthesis of a double-stranded DNA molecule from an RNA mold. The search is targeted towards the genetic code of the CoV that is conserved. CDC recommends to assess for the presence of 1 or several nucleic acid targets specific to SARS–CoV-2.

The probes used are based on the initial gene sequence released by the Shanghai Public Health Clinical Center and School of Public Health, Fudan University, Shanghai, China on Virological.org, and subsequent confirmatory evaluation by additional labs. If the test result is positive, it is recommended that the test is repeated for verification. In patients with confirmed COVID-19 diagnosis, the laboratory evaluation should be repeated to evaluate for viral clearance before being released from observation.

In the United States, the CDC has developed the most widely used SARS–CoV-2 assay. The kit contains PCR primer-probe sets for 2 regions of the viral nucleocapsid gene (N1 and N2) and for the human RNase P gene to ensure the RNA extraction was successful. This assay differs from the WHO primer-probe sets, which target the SARS–CoV-2 RNA-dependent RNA polymerase (RdRP) and envelope (E) genes. Both assays have high analytic sensitivity and specificity for SARS–CoV-2, with minimal cross-reactivity with other circulating strains of coronaviruses, and both use a cycle threshold (CT) of less than 40 as the criterion for positivity.

The lack of an established reference standard, use of differing sample collection and preparation methods, and an incomplete understanding of viral dynamics across the time course of infection, hamper the rigorous assessment of the diagnostic accuracy of the many newly introduced SARS–CoV-2 assays. Conversely, after a patient has had a positive test result, several authorities have recommended obtaining at least 2 negative upper respiratory tract samples, collected at intervals of 24 hours or longer, to document SARS–CoV-2 clearance.

Viral culture

Although viral culture is an important method to evaluate viral infectivity and activity, it is not commonly used in clinical practice because of its low sensitivity and long turn-around time for virus detection. Virus isolation in a culture in the laboratory with a facility for viral culture using Vero-CCL-81 cells is possible. However, this facilities are limited within the country.

Rapid antigen detection tests

Rapid antigen detection test (RDT) detects the presence of viral antigens expressed by the COVID-19 virus in a sample from the respiratory tract. It detects the target antigen as it binds to specific antibodies fixed to a paper strip enclosed in a plastic casing. It generates a visually detectable signal, typically within 30 minutes. However, this test has a limitation in the form of expression occurring only when the virus is actively replicating. It can be used to identify acute or early infection. The test result varies with time from onset of illness, the concentration and the quality of the specimen and the precise formulation of the reagents in the test kits.

From previous experience of the use of these types of kits in Influenza, the sensitivity of these tests is expected to vary from 34-80% for COVID-19 as well. False-positive results may also occur with the antibodies on the test strip also recognize antigens of viruses other than COVID-19, such as human CoV causing common cold. Prototypes of such tests for other novel coronaviruses have not received regulatory approval but are under development. Monoclonal antibodies against the nucleocapsid protein of SARS–CoV-2 have been developed which might form the basis of a future rapid antigen detection test.

Rapid antibody diagnostic test

The principle of the test is based on the detection of the IgM and IgG antibodies, in the blood of patients with COVID-19. The test can be performed with enzyme-linked immunosorbent assays (ELISA). The test
is relatively less complex than other molecular tests and primarily used for the epidemiological purpose in limited situations.\[^{105}\] The IgG antibodies appear late in the second week after onset of symptoms, while the majority of them show futures of recovery.\[^{106,107}\]

Thus the use of this test in making clinical intervention and in the prevention of transmission of the disease remains limited. The negative result also does not exclude recent SARS–CoV-2 exposure and infection.\[^{105}\] Several factors, like age, malnutrition, the severity of the disease, and immunosuppressed state because of medications or HIV like disease, affects the formation of the antibodies.\[^{106,107}\] However, the test may be combined in reporting with RT-PCR report with the presence or absence of antibody response.\[^{106,107}\] The possibility of cross-reactivity and false positivity of COVID specific antibody with other human CoV can not be excluded.\[^{88,107,108}\]

The information about the protective nature of the antibody is still emerging; however, antibodies against S-protein may be protective, and plasma from recovered patients show neutralizing activity.\[^{108}\] The test may help in analyzing antibody responses to COVID-19, a critical response in the development of vaccines. The test can be used for detecting the epidemiological extent of infection missed during active surveillance efforts, analyzing the attack rate, and infection fatality rate.

**Ancillary diagnostic test**

Radiographic imaging: The plain chest radiography is still the early and easy ancillary supportive test in COVID-19 management. The bilateral pneumonia is the most common finding ranging from 11.8-100%. The bilateral findings are more common than a unilateral focus.\[^{82,109}\]

Computed tomography of thorax appears more sensitive than plain radiography. A large study have shown that typical imaging features, include ground-glass opacities (86.1%) or mixed ground-glass opacities and consolidation (64.4%), vascular involvement in the lesion (71.3%), and traction bronchiectasis (52.5%). The lesion on CT images had more peripheral distribution (87.1%), bilateral involvement (82.2%), lower lung predominant, and multifocal each in 54.5%.\[^{109}\] Studies reported that CT chest might be more sensitive than serial nasopharyngeal sampling and RT-PCR test at a single-point diagnosis of COVID-19.\[^{111,112}\] Although artificial intelligence may help in distinguishing COVID-19 from other etiologic agents of community-acquired pneumonia,\[^{113}\] but the CT findings, do not exclude a co-infection or an alternative diagnosis.\[^{114}\]

**Other Biomarkers Associated with COVID-19**

Decreased albumin, elevated C-reactive protein, and elevated lactate dehydrogenase levels, and lymphopenia were other laboratory parameters associated with COVID-19.\[^{115}\] Increased erythrocyte sedimentation rates, elevated aspartate aminotransferase, alanine aminotransferase, and creatinine kinase levels, leukopenia, leukocytosis increased bilirubin and creatinine levels were associated with severe cases and multi-organ involvements.\[^{50,51,116}\] These biomarkers are an indication of the inflammatory host response to SARS–CoV-2, as observed in any patients with sepsis.\[^{117}\] It is difficult to predict clinical outcomes with any identified single or combination of biomarkers currently exists.

In summary, COVID-19 is a novel Beta CoV infection which has genomic homology with Bat CoV and transmitted to human beings through intermediate host. Person to person transmission in the human being is a major mode of transmission, which lead to pandemic from a small cluster outbreak from Wuhan city of China. The lung is primarily involved. However, kidney involvement is frequent and is an independent risk factor for mortality with this novel CoV infection. With the increasing stage and severity of AKI, the hazard ratio of death of patients with COVID also increases. The overall case-fatality rate is reportedly 2.3% in confirmed cases, about 15% in elderly patients, in particular those aged ≥80 years, and 8% in people who are 70-79 years of age.\[^{118}\] The mainstay of therapy of COVID-19 is supportive and preventive requiring quarantine and waiting self recovery.

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**Conflicts of interest**

There are no conflicts of interest.

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Chronic Kidney Disease and Hypertension with Reference to COVID-19

The prevalence of chronic kidney disease (CKD) is very high in all parts of the world, including India. Although there is no literature available, being in an immunocompromised state, these patients are likely to be at high risk of COVID-19. It is likely that many CKD patients will also acquire SARS-CoV-2 infection. The data as coming from various countries is showing that elderly patients especially those with associated co-morbidities of diabetes mellitus, hypertension, or cardiovascular disease are not only at a higher risk for this infection but the severity of infection is also more.[1] Diabetes and hypertension being the commonest cause of CKD, many of these patients will also have associated CKD. While On other hand, CKD patients have an underlying immunosuppressed state and may not mount an aggressive immune response to this infection, implying that they may have different pattern of presentation of the disease. In a study from Wuhan city, patients on hemodialysis (HD) with COVID-19 had less lymphopenia, and lower serum levels of inflammatory cytokines. These patients also had less symptomatic disease as compared to patients with COVID-19 infection.[1] Therefore, besides avoiding unnecessary hospital visits, physicians should put more emphasis on providing consults using information technology/telemedicine. In India, till recently, there were no guidelines or legislation to provide consults by telemedicine. However, the Ministry of Health and Family Welfare has recently released guidelines for physicians to provide consultations through telemedicine.[2]

It is anticipated that few patients of CKD will experience episodes of acute kidney injury (AKI) following COVID-19 infection, and the renal function will further deteriorate. Such a decline in kidney function will however depend upon the severity of the infection. SARS-CoV-2 may affect the kidney directly through angiotensin-converting enzyme 2 (ACE2) receptors causing direct injury, glomerular injury by affecting effector T cell or immune-complex formation, and as a part of cytokine storm after virus-induced sepsis.

CKD Management and COVID

Most CKD patients are on multiple drugs to manage anemia, metabolic bone disease (MBD), fluid status, diabetes, and hypertension. Anti- hypertensives include diuretics, calcium channel blockers, centrally acting drugs, beta-blockers, alpha-blockers, angiotensin- converting enzyme inhibitor, and angiotensin receptor blockers. There may be a concern about the safety of all these drugs.

Anemia management?

Erythropoietin (EPO) is a multi-functional cytokine, which exerts erythropoietic effects but also carries anti-apoptotic and immune-modulatory activities upon binding to two distinct receptors, which are expressed on erythroid, parenchymal, and immune cells, respectively. The effect of erythropoietin on viral replication, particularly COVID-19, is not known. At present, there is no evidence to suggest stopping or changing EPO doses. Oral iron therapy should be continued, and the use of intravenous iron should be discouraged during COVID-19.

Management of CKD-MBD

Medications for CKD-MBD should be continued as before unless there are specific contraindications that appear during the management of COVID 19 infection. As of date, there are no interactions or contraindications to the use of these drugs during COVID-19. Some patients with CKD-MBD may require pain killers.

There are unconfirmed reports of patients who are on non-steroidal anti-inflammatory drugs (NSAIDs) having more severe disease compared to acetaminophen/ paracetamol. However, we feel that this may be because patients with more severe symptoms are likely to take NSAIDs (versus acetaminophen). This is one more reason why the CKD patients should avoid taking NSAIDs and instead should take paracetamol.

COVID-19 and renin-angiotensin - aldosterone system (RAAS)?

Angiotensin-converting enzyme 2 (ACE2) functions as a receptor for both severe acute respiratory syndrome coronavirus 1 and 2 (SARS-CoV-1 and SARS-CoV-2) resulting in possible interaction between the renin–angiotensin–aldosterone system (RAAS) and COVID-19.[1] COVID-19 viral S protein gains entry into the target cells by getting attached to the surface receptor called angiotensin-converting enzyme-2 (ACE-2) receptor of the cardio-pulmonary cells. As the use of ACE inhibitors/angiotensin receptor blockers (ACEI/ARB) can increase the expression of ACE-2 receptors, [Figure 1]
these patients may be at risk of more severe infection due to the availability of increased receptors.\(^4,5\)

With the evidence of higher mortality in the patients of hypertension, diabetes, cardiovascular disease, and old age\(^6\), there is a hypothesis raised, whether the use of ACEi/ARB, which is commonly used in these subsets of patients, can increase the risk and potential threat to COVID-19 infection. This will have a major impact on the management of hypertension, and people are concerned regarding the use of RAAS blockers. However, there are guidelines from various societies, including the European Society of Cardiology, stating that there is no such evidence of ACE-2 activity and COVID-19 associated mortality [Figure 2]. It has been pointed out that there is no data on how many of those who died with COVID-19 were on ACEi/ARBs.\(^7\)

Patients are likely on these drugs because of associated co-morbidities like diabetes, hypertension, or cardiovascular disease, which may have increased their mortality. In fact, it was shown that COVID-19 spike protein led to the down-regulation of ACE-2 and more severe lung injury in mice that could be attenuated by the administration of an ARB.\(^8\) It was also explained that high angiotensin II (in severe cases or in the absence of ACEI/ARB) could open

| Society                                      | Summary of recommendations                                                                 | Last Statement Update |
|----------------------------------------------|---------------------------------------------------------------------------------------------|----------------------|
| European Society of Hypertension             | Recommend continuing ACEis/ARBs due to lack of evidence to support differential use in COVID-19 patients. In those with severe symptoms or sepsis, antihypertensive decisions should be made on a case-by-case basis taking into account current guidelines | March 12, 2020       |
| European Society of Cardiology Council on Hypertension | Strongly encourage continuing ACEis/ARBs due to lack of evidence to support discontinuing  | March 13, 2020       |
| Hypertension Canada                          | Recommend continuing ACEis/ARBs due to lack of evidence that patients with hypertension or those treated with ACEis/ARBs are at higher risk of adverse outcomes from COVID-19 infection | March 13, 2020       |
| Canadian Cardiovascular Society              | Strongly encourage continuing ACEis/ARBs and Angiotensin Receptor Neprilysin Inhibitors due to a lack of clinical evidence to support withdrawal of these agents | March 15, 2020       |
| The Renal Association, United Kingdom        | Strongly encourage continuing ACEis/ARBs due to unconvincing evidence that these medications increase risk | March 15, 2020       |
| International Society of Hypertension       | Strongly recommend that the routine use of ACEis/ARBs to treat hypertension should not be influenced by concerns about COVID-19 in the absence of compelling data that ACEis/ARBs either improve or worsen susceptibility to COVID-19 infection nor do they affect the outcomes of those infected | March 16, 2020       |
| American College of Physicians              | Encourage continuing ACEis/ARBs because there is no evidence linking them to COVID-19 disease severity, and discontinuation of antihypertensive therapy without medical indication could in some circumstances result in harm | March 16, 2020       |
| Spanish Society of Hypertension              | Recommend that ACEis/ARBs should not be empirically stopped in patients who are already taking them; in seriously ill patients, changes should be made on a case-by-case basis | March 16, 2020       |
| American Heart Association, Heart Failure Society of America, American College of Cardiology | Recommend continuing ACEis/ARBs for all patients already prescribed them | March 17, 2020       |
| European Renal Association - European Dialysis and Transplant Association | Recommend continuing ACEis/ARBs in COVID-19 infection patients due to a lack of evidence to support differential use and the discontinuation of ACEis/ARBs in COVID-19 patients | March 17, 2020       |
| American Society of Pediatric Nephrology     | Strongly recommend continuing ACEis/ARBs until new evidence to the contrary becomes available | March 17, 2020       |
| High Blood Pressure Research Council of Australia | Recommend continuing routine use of ACEis/ARBs. Patients should not cease blood pressure lowering medications unless advised to do so by their physician | March 18, 2020       |
| Australian Diabetes Society                  | Recommend that usual antihypertensive therapy is continued given that speculation about risk of ACE inhibitors and ARBs is purely theoretical | March 29, 2020       |

Figure 2: Professional Societies Recommendations on use of ACEi/ARB (Adapted from NephJC http://www.nephjc.com/news/covidace2)
up the ACE-2 receptor by unbinding of ATR-1, thereby making it available for COVID-19 to attach. These findings suggest a protective role of ARB in COVID-19 associated lung injury and give rise to the hypothesis that primary activation of the RAAS in patients, rather than its inhibition, renders them more prone to a deleterious outcome.[6,9] Therefore, we suggest continuing ACEI and ARBs for anti-hypertensive and renoprotective purposes. Other anti-hypertensive drugs should also be continued as before unless there is some specific contraindication that appears during the infection like hypotension.

The utility of hydroxychloroquine

Hydroxychloroquine, which is an immunomodulator, is shown to reduce viral activity in vitro in SARS-CoV-2 infected vero cells.[10] In addition, hydroxychloroquine has been shown to significantly reduce viral load in nasopharyngeal swabs in 20 French patients with COVID-19.[11] So, hydroxychloroquine has both direct anti-viral effects and anti-inflammatory effects. Until further evidence in the form of clinical trials, it appears theoretically effective in combating severe phase of COVID-19 infection. While its role as a prophylactic therapy is uncertain, it is increasingly being advocated by many nations. Indian Council of Medical Research (ICMR) has also recommended the use of hydroxychloroquine in selected individuals.[12]

Though hydroxychloroquine is usually safe, there are side effects of this drug that all the physicians should be aware of. The short-term side effects include nausea, gastrointestinal disturbance, and prolongation of QT interval, whereas the retinal toxicity is the most dreaded complication over long term use. In addition, there may be significant drug interactions with this drug. There are no well-defined recommendations for dose modification according to the glomerular filtration rate. Therefore, hydroxychloroquine may be used judiciously in CKD cases.

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Conflicts of interest

There are no conflicts of interest.

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Glomerular Diseases with Reference to COVID-19

Abstract
COVID pandemic affected every individual across the world. Patients with primary glomerular disease and glomerular disease secondary to systemic diseases who are on moderate to high doses of immunosuppression are at an increased risk of COVID because of their immunosuppressed state. The data to quantify the degree of risk in relation to the amount of immunosuppression or their duration of use is not robust. The patients on immunosuppression need to modify the drugs balancing the risk relapse and flare of the disease, simultaneously minimizing the risk of developing COVID. We tried to develop a guideline about the modification of the treatment regimen in such conditions.

Keywords: Immunosuppression, primary glomerular disease, secondary glomerular diseases

Introduction
Patients with a glomerular disease in reference to COVID-19 have two broad issues. First, in view of reports of proteinuria and hematuria in patients with COVID-19, there is a possibility of glomerular disease secondary to COVID-19; and second, patients with the glomerular disease may develop COVID-19. At present, there is insufficient evidence to suggest that COVID-19 itself can produce secondary glomerular disease, though being a viral infection, potentially it is possible. Therefore, the main issue is COVID-19 infection in patients with the preexisting glomerular disease and handling their immunosuppression. Patients with primary glomerular disease and glomerular disease secondary to systemic diseases like systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), who are on moderate to high doses of immunosuppression are at an increased risk of COVID because of their immunosuppressed state.[1] However, as of now, there is a paucity of data to quantify the degree of risk in relation to the amount of immunosuppression or their duration of use. Therefore, what is being suggested is based on the extrapolation of evidence from other infections.

A simple way to evaluate these patients is to classify them into newly diagnosed patients, and those on follow-up on immunosuppressant medications, separately.[2]

A. For newly diagnosed patients:
   a. We suggest that newly diagnosed patients with primary and secondary glomerular disease should be managed on their merit if they do not come under category of “suspected” COVID or have a positive test for COVID-19. However, these patients should receive the Pneumococcal vaccine to reduce the chances of secondary Pneumococcal pneumonia
   b. If a patient is suspected or positive COVID and needs immunosuppressive medication, we suggest using immunosuppression, after explaining the risk-benefit ratio to the patient.

B. For follow-up patients:
   Follow-up patients on immunosuppressants may be in the induction phase or the maintenance phase of the treatment.
   a. Induction phase:
      As there is currently no policy that non-suspected patients should be tested for COVID-19 before each dose of induction therapy, we suggest that patients of the induction phase should get standard induction medication unless directed otherwise by their attending renal team. All patients coming to the admission for induction medication unless directed otherwise by their attending renal team. All patients coming to the admission should receive the Pneumococcal vaccine to reduce the chances of secondary Pneumococcal pneumonia.

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hospital for induction therapy should be triaged on arrival before any infusion to exclude symptoms of active COVID-19 infection and to check for raised temperature. Those who are considered to have a “suspected” COVID-19 infection can then be seen in a separate area away from other patients and appropriate treatment plans made. If the patient is not able to come to the hospital due to lock-down for getting an intravenous (iv) injection of induction immunosuppression (Cyclophosphamide), we suggest the following options:

1. In patients of vasculitis, we suggest switching over to oral cyclophosphamide temporarily under monitoring another option is using oral mycophenolate mofetil (MMF) especially in patients with low risk of relapse[3]

2. In patients with SLE, if the patient is on iv cyclophosphamide, he/she can be easily changed to oral MMF, a well-established alternative to iv cyclophosphamide as induction therapy.[4]

As there is no experience that how COVID-19 infection could behave during rituximab therapy, it will be wise to avoid using rituximab in such uncertain situation. In general, to reduce infection risk, we suggest minimizing steroids promptly.

We recommend a risk stratification approach to help manage these patients. Some patients, particularly those on steroids, iv cyclophosphamide, and biologics, will be significantly immunosuppressed and should, therefore, be considered “high risk”. This is particularly true in the induction phase of their treatment. Others on steroid monotherapy will be at intermediate risk.

b. Maintenance Phase

Patients of glomerular disease on maintenance immunosuppression, if doing well, and are not in COVID-19 “suspect” or “positive” group, should continue to take their maintenance medication unless directed otherwise by their treating team. Immunosuppressive therapy needs to be reviewed on a case by case basis, balancing the risk of inadequately treated disease, or acute relapse, against the risk of the effect of COVID-19 infection in the individual patient. Patients on long term glucocorticoids SHOULD NOT stop these abruptly. Patients receiving hydroxychloroquine should continue this as it may afford some protection against COVID-19. All patients with glomerular disease if fall in the category of “suspected” COVID-19 should be tested as per standard guidelines. Inpatients who are COVID-19 positive, the nephrologist may consider modifying maintenance immunosuppression regimens on a case by case basis. In the case of long-acting rituximab maintenance regimens, delaying intervals between rituximab infusions could be considered for patients where the risk of disease progression or flare is deemed low. Lower doses of rituximab may be considered as given evidence from the Mainritsan study suggesting equivalent efficacy.[5] Children with idiopathic nephrotic syndrome who are on alternate day prednisone and develop symptoms of upper respiratory tract infection (URTIs) should not be switched to daily prednisone as per usual practice.

Where standard immunosuppression protocols are modified on a balance of risk, we recommend to optimize surveillance for relapse with increased clinical assessment, autoantibody screening, and lymphocyte subset analysis where possible, though one must realize that in the situation of COVID-19 pandemic, such close monitoring and repeated test may not be logistically possible.

Policy on Isolation for Patients with Glomerular Diseases

We suggest that patients of glomerular disease on immunosuppression should be risk-stratified into the following three groups:

a. Group A (High Risk):
   - Those patients of glomerular disease who are currently on induction immunosuppressive medications, whether steroid or cytotoxic medication, are at a high risk because of the degree of higher immunosuppressive agents. They should all be advised to follow strict social distancing, hand hygiene, and face mask. If they reside in the hot spot area in reference to COVID-19, it will be a better idea to self-isolate for few weeks
   - Are currently on stable maintenance IS but whose additional comorbidities make them susceptible to a severe course in COVID-19— (a) age >70 years (b). Those with any non-autoimmune underlying co-morbidity of COAD, CVD, hypertension, or diabetes mellitus.

b. Group B (Moderate risk):

Those patients of glomerular disease who are currently on stable maintenance immunosuppression (single drug) but whose additional comorbidities make them susceptible to a severe course in COVID-19— (a) age >70 years (b). Those with any non-autoimmune underlying comorbidity of COAD, CVD, hypertension, or diabetes mellitus; will fall in this group. These patients should follow strict social distancing, hand hygiene, and face mask. We recommend not to stop medications as this can lead to the relapse of the disease or nephrotic syndrome.

C. Group C (Low Risk)

We suggest that these patients may not require self-isolation in the first instance but should follow all hygiene measures listed below. These include:
(1) Children with idiopathic nephrotic syndrome who are on levamisole or low dose alternate-day prednisone
(2) Children with idiopathic nephrotic syndrome who are infrequent relapsers
(3) Patients <60 years who are generally well and whose disease (SLE, AAV, MCD, FSGS, membranous nephropathy, or IgA nephropathy) have been stable for >6 months and off immunosuppression
(4) SLE patients who are on hydroxychloroquine alone.

These recommendations are and will remain dynamic and might change as new data emerge.

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Conflicts of interest
There are no conflicts of interest.

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COVID 19 and Acute Kidney Injury

Abstract
Coronavirus disease 19 (COVID-19) is caused by severe acute respiratory syndrome-corona virus (SARS-CoV-2), a beta coronavirus, mainly involves the respiratory tract, and the clinical features simulate to a severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) of the past. The genome of the SARS-CoV-2, isolated from a cluster-patient with a typical pneumonia after visiting Wuhan, had 89% nucleotide identical with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV. It enters the respiratory tract through angiotensin converting enzyme-2 (ACE2) receptors on alveoli. It may induce lung injury through direct cytopathic effect, involving effector T cells or causing sepsis and inducing cytokine storm. With a similar mechanism, it can cause acute kidney injury (AKI). The overall incidence of AKI is 5.1%, and AKI is an independent risk factor for mortality. The hazard ratio of death increases with the increasing severity of AKI. Management of COVID-19 with AKI is primarily supportive care, and at present, there are no evidence based effective antivirals for the treatment.

Keywords: Acute kidney injury, coronaviruses disease, COVID-19, outcomes, severe acute respiratory syndrome

Introduction
Coronavirus disease-19 (COVID-19) is caused by a beta-coronavirus, which has been named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) on February 11, 2020, by the International Committee on Taxonomy of viruses by the World Health Organisation (WHO). It has been called SARS-CoV2 because the primary manifestations of the disease are severe respiratory tract involvement, similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

Worldwide situation
The recent outbreak of COVID-19, in December 2019 in Wuhan City, Hubei province of China, started with a cluster of pneumonia patients gradually gripping the world leading to declaration as a pandemic by WHO in March, 2020. As of the date on March 25, 2020, WHO reported a total of 3,75,498 confirmed cases, and 16,362 deaths from 196 countries. After China, it spread to the United States, Europe, and Asia, and now increasing cases are being reported from Europe and other parts of Asia outside China. A total of 1,990 confirmed cases with 65 deaths have been reported from the South-East Asia Region.

India specific situation
As of March 23, 2020, the Indian Council of Medical Research data showed a total of 18,383 samples from 17,493 individuals had been tested, and 415 individuals were positive for SARS-CoV-2, and 7 deaths have been claimed because of COVID-19 infection. In an opinion by the Director of Center for Disease Dynamics, Economics and Policy (CDDEP), applying mathematical models used in the USA or the United Kingdom to India points to a possible 300 million (30 crore) cases in India, out of which 10 crores will face severe COVID infection, if appropriate severe control measures are not taken. Looking at the incidence of 5.1% of AKI in severe cases, there may be the potential of 5.1 million AKI patients because of COVID-19, and many of them may require renal replacement therapy (RRT). It is not surprising that if community spread happens in India, with limited resources and health infrastructure, it may be challenging to combat the situation of patients with multiorgan failure and AKI. However, India can handle the COVID-19, and its affects if the disease spreads over a long period of time.

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Moreover, COVID-19 appears more contagious than SARS and MERS, spreads by human-to-human transmission via droplets infections and fomites. The incubation period ranges from 2 days to 2 weeks (usually 3 to 7 days).

**AKI and SARS-CoV-2: Clinical Manifestations**

Though COVID-19 manifests primarily as diffuse alveolar damage, interstitial pneumonia, and acute respiratory failure, the involvement of other organs such as the kidney, heart, digestive tract, blood, and nervous system is potentially possible.\(^8\)\(^-\)\(^10\) It has been reported that SARS-CoV and MERS-CoV had infected more than 10,000 people in the past 2 decades, with mortality rates of 10% and 37%, respectively.\(^11\)\(^,\)\(^12\) In the previous reports of SARS and MERS-CoV infections, acute kidney injury (AKI) developed in 5% to 15% cases and carried a high (60%–90%) mortality rate.\(^13\) A study reported that although AKI was uncommon in SARS but accounted for the fiercely high mortality of 91.7%, notably 33 out of 36 cases died.\(^14\) Kidney involvement was a strong and independent predictor of mortality during the SARS and MERS outbreak, suggesting the similar situation for the kidney involvement with COVID-19 infection as well.

The incidence of AKI with COVID-19 has been reported varying from 3%–9%.\(^15\)\(^-\)\(^18\) A large prospective study has reported the overall incidence of 5.1%.\(^19\) In a study of 59 COVID-19 patients with severe cases and 3 deaths, Li et al.\(^19\) found that 34% of patients had proteinuria on the first day of admission, and 63% developed proteinuria during the hospital stay. Nineteen percent of people showed an elevated level of serum creatinine. Blood urea nitrogen (BUN) was elevated in 27% patients and in two-thirds of patients who died. Each one of those (27/27) who had computerized tomography (CT) abdominal scan showed radiographic abnormalities of the kidneys with reduced density suggesting inflammation and edema. The study also emphasized that renal impairment may be an independent factor of mortality.

In another larger prospective study, Cheng Y et al.\(^7\) reported 701 patients (median age 63 years with interquartile range, 50–71 years, and 367 males) admitted in a tertiary teaching hospital following the outbreak of COVID-19 in Wuhan city of China. A total of 113 (16.1%) died in the hospital, and the median time to death was 6 days (IQR 3–12) days. On admission, 43.9% of patients had proteinuria, and 26.7% had hematuria. The prevalence of elevated serum creatinine, elevated BUN, and estimated glomerular filtration (eGFR) under 60 ml/min/1.73m\(^2\) were 14.4%, 13.1% and 13.1%, respectively. Overall, AKI was reported in 5.1% of patients. Patients with kidney disease had a significantly higher risk of in-hospital death. Cox proportional hazard regression confirmed that elevated baseline BUN (3.97, 2.57–6.14), and elevated baseline serum creatinine (hazard ratio: 2.10, 95% CI: 1.36–3.26) was an independent predictor of mortality. It has also been observed that the hazard ratio for mortality also increases with the staging of AKI from 1.9 in stage 1, 3.51 in stage 2, and 4.38 in stage 3 AKI. The hazard ratio of mortality also increased with the degree of proteinuria and hematuria. These factors remain significant factors for in-hospital death after adjusting for age, sex, disease severity, comorbidity, and leukocyte count. The incidence of in-hospital mortality in patients with elevated baseline serum creatinine was 33.7%, significantly higher than patients with normal baseline serum creatinine (13.2%). However, the major limitation of the study was that baseline coexisting chronic kidney disease (CKD) could not be assessed.

**Mechanism of AKI with COVID-19**

The mechanism of kidney involvement is at present speculative and appears multifactorial. The susceptible host, particularly elderly and people with underlying diseases like hypertension, cardiac diseases, bronchial asthma, diabetes, etc., are at a risk of severe disease. Like any other viral infection causing kidney injury, the direct viral cytopathic effect on kidney is a postulated mechanism. The virus does not show any evidence of renal tropism. The viral nucleic acid material of CoV in blood and urine in SARS-CoV infection as well as in COVID-19 patients, supports this hypothesis.\(^20\)\(^,\)\(^21\) Recently, SARS-CoV-2 from the urine sample of an infected patient has been isolated, suggesting the kidney as the target of this novel coronavirus.\(^22\)

The molecular study showed SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptor for cell entry like SARS-CoV. ACE2 and dipeptidyl peptidase-4 (DPP4), both expressed on renal tubular cells, were identified as binding partners for SARS-CoV and MERS-CoV, respectively.\(^23\)\(^,\)\(^24\) ACE2 expression is 100-fold higher in kidney tissues than the lung.\(^19\) However, still clinical observation is different that there is more severe lung injury than kidneys in SARS and SARS-CoV-2 as well.

The normal glomerular pathology on microscopy and the absence of electron-dense deposit on ultrastructure microscopy in SARS-CoV patients, do not support the hypothesis of the immune complex-mediated glomerular injury though direct effector T cell-mediated injury could be another postulated mechanism.\(^14\) Another important mechanism appears to be virus-induced sepsis and the release of cytokines in circulation leading to severe inflammatory response, hypotension, hypoxia, shock, and the aggravation of target organ injuries, including kidneys as well. The clinical pictures of patients with COVID-19 with sepsis supports this hypothesis.

Most of the patients had mild symptoms with fever, sneezing, cough, sputum, and dyspnea, which indicate severe lower respiratory tract injury. The manifestations
with severe COVID-19 are multi organ involvement, which includes respiratory events such as severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of other organs. The functional changes were expressed as the laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia. These patients may require intensive care unit treatment. Huang et al.\(^ {21}\) revealed that all of their 41 patients in the study had pneumonia with bilateral lobular and sub-segmental consolidation on CT, and 32% of them required intensive care. The patients requiring intensive care had higher plasma cytokine levels of (interleukin [IL]-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-inducing protein-10, monocyte chemoattractant protein 1, macrophage inflammatory protein-1a, and tumor necrosis factor \(\alpha\)) on admission. These findings suggest that some of them may benefit from the removal of cytokines during continuous renal replacement therapy (CRRT).

### Diagnosis of AKI

The diagnostic criteria and AKI staging is not different than AKI in other situations.\(^ {25}\) The diagnosis of COVIT-19 itself is based on the history of contact, clinical and laboratory evidence with hemogram, biochemical parameters, chest imaging with CT and virological examination.\(^ {26}\) The confirmation of the diagnosis requires a nucleic acid amplification test with reverse transcriptase polymerase chain reaction (RT-PCR) and other techniques. Many in-house and commercial available nucleic acid detection assays for COVID-19 are available.\(^ {26}\) Next-generation gene sequencing can also be used. WHO appointed many referral laboratories in different countries.\(^ {27}\) A serological test has also been developed and allowed the detection of a cluster of cases in Singapore.\(^ {28}\)

### Treatment

At present, the management strategies of COVID-19 with AKI is primarily conservative in the form of good hydration, nutritional support, paracetamol for fever, headaches and body aches, and antibiotics in the case of secondary bacterial infection only, with aiming for the self-recovery. Along with patient treatment, spread to others also should be given importance. The patient with respiratory distress may require oxygen therapy and intensive care with ventilatory support in the case of acute respiratory distress syndrome. All confirmed COVID-19 patients need to be isolated. An N95 fit-tested respirator and protective clothing and equipment are essential for patients, and the caregivers should also use appropriate approved personal protective equipments (PPEs).

There is no evidence-based effective antiviral therapy available. In a prospective study of AKI with COVID-19, the three most used medicines were antivirals (73.0%), antibiotics (71.0%), and glucocorticoid (36.9%). Antivirals showed mortality benefit, and the glucocorticoids did not, which is possible because clinicians have used steroids mainly in the terminally sick patients. The varieties of anti viruses were used, including arbidolhydrochloride, ganciclovir, interferon, lopinavir and ritonavir, oseltamivir, and ribavirin. However, there was no significant difference on AKI with these therapies.\(^ {27}\)

The most recent New England Journal of Medicine (NEJM) study of a randomized controlled trial\(^ {29}\) showed no mortality benefit of treatment with lopinavir-ritonavir combination (19.2%) as compared to the standard of care arm (25%). The median time of clinical improvement was only one day shorter in the treatment arm. Lopinavir-ritonavir treatment was stopped early in 13.8% because of adverse events. With some success story with remdesivir in COVID-19 treatment, a clinical trial is currently going on.\(^ {30}\) Chloroquine phosphate showed some efficacy against COVID-19 associated pneumonia in a multicentre clinical trial conducted in China.\(^ {31}\) The National Taskforce for COVID-19 by the ICMR recommended the use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection for healthcare workers involved in the care of suspected or confirmed cases of COVID-19 in a dose of 400 mg twice a day on Day 1, followed by 400 mg once weekly for next seven weeks; and for household contacts of laboratory-confirmed cases in the dose of 400 mg twice a day on Day 1, followed by 400 mg once weekly for next three weeks; to be taken with meals. The warning with this advisory also mentioned that the health care workers should not have a false sense of security with this chemoprophylaxis and other preventive measures should remain continued.\(^ {32,33}\)

Few retrospective analyses showed benefit with the use of glucocorticoids in SARS-CoV infection.\(^ {34,35}\) Metaanalysis on the use of glucocorticoids in previous SARS-CoV infection do not support the use of glucocorticoids in COVID-19 as well. In a meta-analysis of corticosteroid use in patients with SARS, four studies showed harm with higher psychosis, diabetes, avascular necrosis, and delayed viral clearance.\(^ {36}\) WHO does not recommend the use of steroid expecting potential inhibition of viral clearance and prolongation of the duration of viremia.\(^ {17}\)

### Experimental strategies

The use of convalescent plasma showed speedy clinical recovery in some patients with COVID-19 in China.\(^ {21}\) Two trials, an open-label, non-randomized clinical trial (NCT04264858) and another multicentre, randomized, and parallel-controlled trial (ChiCTR2000029757) on the efficacy of convalescent plasma in patients with COVID-19, are awaiting results.

In the modern era of monoclonal antibodies directed therapy, the researchers showed encouraging results with...
the use of monoclonal antibodies in the treatment of SARS infection as well. An in-vitro study showed neutralizing activity in an assay with a monoclonal antibody directed against the Ras-binding domain of the S-protein of Middle East respiratory syndrome coronavirus (MERS-CoV). However, no such evidence is available against COVID-19.

Inflammatory cytokines levels were extremely high in critically sick patients with infection.[21] Tocilizumab, a monoclonal antibody against the IL-6 receptor, may be of benefit; however, its use in treatment requires more evidence. The safety and efficacy of tocilizumab in COVID-19 infection are also under clinical trial (ChiCTR2000029765).

**Extracorporeal therapy**

The indication of dialysis remains standard as for any other AKI patients. CRRT, with high volume hemofiltration that will be capable of removing inflammatory cytokines, appears theoretically advantageous. CRRT was successfully used in the treatment of SARS, MERS, and sepsis in the past.[14,30] A study showed significant improvement in the Sequential Organ Failure Assessment scores at day 7 in patients with sepsis treated with high-volume hemofiltration and removal of IL-6.[19]

In summary, COVID-19 infection may involve kidneys besides the respiratory tract leading to proteinuria, hematuria, and AKI. AKI is an independent risk factor for mortality. With the increasing stage and severity of AKI, the hazard ratio of death of patients with COVID-19 also increases. The management strategies applied for AKI in COVID-19 are supportive only. COVID-19 patients need to be isolated to prevent the spread of infection.

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**Conflicts of interest**

There are no conflicts of interest.

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General Guidelines for Dialysis with Reference to COVID-19

Note: Most of the parts of the guideline has been accepted by Ministry of Health and Family Welfare (MOHFW), Government of India and has been put on the website of MOHFW https://www.mohfw.gov.in/pdf/RevisedGuidelinesforDialysissofCOVID19Patients.pdf. Last accessed on 15 May 2020.

COVID-19, a disease caused by a novel corona virus (SARS CoV-2), is currently a pandemic, which produces high morbidity in the elderly and in patients with associated comorbidities. Chronic kidney disease stage-5 (CKD-5) patients on dialysis [maintenance hemodialysis (MHD) or continuous ambulatory peritoneal dialysis (CAPD)] are also vulnerable group because of their existing comorbidities, repeated unavoidable exposure to the hospital environment, and immunosuppressed state due to CKD-5. These patients are therefore not only more prone to acquire infection but also develop severe diseases as compared to general population.[1,2]

Patients on regular dialysis should adhere to prescribed schedule and not miss their dialysis sessions to avoid any morbidity in the elderly and in patients with associated comorbidities, repeated unavoidable exposure to the hospital environment, and immunosuppressed state due to CKD-5. These patients are therefore not only more prone to acquire infection but also develop severe diseases as compared to general population.[1,2]

Patients on regular dialysis should adhere to prescribed schedule and not miss their dialysis sessions to avoid any emergency dialysis.[2,1]

There will be three situations of patients who require dialysis; patients already on maintenance dialysis, patients requiring dialysis due to acute kidney injury (AKI) and patients critically ill requiring continuous renal replacement therapy (CRRT).

General Guidelines for Administration[3,4]

1. State/UT should identify and earmark atleast one hemodialysis facility with adequate number of dialysis machines, trained staff, reverse osmosis (RO) water system and other support equipment as preparatory fixed-point dialysis unit in case of rise of COVID-19 epidemic
2. Health departments may issue directives to the district administrations allowing easy movements of these patients (with one attendant) to dialysis facility. Patients who do not have private vehicles, government run transport system should be organized for facilitating transport of these patients. Patients should use their hospital papers as pass to commute to the dialysis unit
3. District administration should ensure that service providers for the dialysis consumables, both for MHD and CAPD should be allowed to deliver the material to the hospital or home as the case may be.

General Guidance for Dialysis Unit[3-5]

1. Adequate medical supplies such as dialysate, dialyzers and tubing, catheters, fistula needles, disinfectant and medicines, etc., must be ensured in adequate quantity
2. A sign board should be posted prominently in the local understandable language as well as Hindi and English asking patients to report any fever, coughing or breathing problem in dialysis unit and waiting area. The information including images for education can be obtained on the International Society of Nephrology website https://www.theisn.org/covid-19
3. All hemodialysis units should educate their personnel in hemodialysis units; including nephrologists, nurses, technicians, other staff and all patients undergoing MHD along with their care givers about COVID 19
4. We recommend that All universal precautions must be strictly followed
5. All staff should strictly follow hand hygiene (seven steps) with soap and water for 20 s before handling any patient and in between two patients. If soap and water are not readily available, use a hand sanitizer that contains at least 60% alcohol. If hands are visibly soiled or dirty, they should be first washed with soap and water and then an alcoholic hand rub used. Avoid touching your eyes, nose, and mouth with unwashed hands
6. Medical and support staff treating infected patients should be monitored for COVID infection at the dialysis facility and should take necessary action if found infected
7. Dialysis units should organize healthcare workers shift duties in a way that work of dialysis unit is not affected
8. All hemodialysis units should be aware of the testing, triage, and notification policy recommended by the local health authorities, regional medical councils and the Union Ministry of health and Family welfare
9. Some of the dialysis unit staff should be trained for donning and doffing of Personal Protective Equipment (PPE) so that they can be used for treatment of COVID-19 positive patients
10. All staff should be trained for cough etiquette, hand hygiene and proper use and disposal of mask, gown, and eye glasses and the need to protect themselves
11. All patients with suspected COVID-19 be tested as per the local health authorities’ guidelines
12. Patients with suspected or positive COVID-19 should be referred to COVID-19 care team as per local guidelines.

Guidelines for Hemodialysis

I. For Patients[2,4,5]
   a. Before Arrival to Dialysis Unit
      1. All units should instruct their patients to recognize early symptoms of COVID-19 (Recent onset fever, Sore throat, Cough, recent Shortness of breath/dyspnea, without major interdialytic
weight gain, rhinorrhea, myalgia/bodyache, fatigue, and Diarrhea) and contact dialysis staff before coming to dialysis center. The unit needs to make necessary arrangement for their arrival in the screening area.

2. Patients, who are stable on MHD may be encouraged to come to the unit alone without any attendant

b. Screening Area

1. We recommend that dialysis unit should have a designated screening area, where patients can be screened for COVID-19 before allowing them to enter inside dialysis area

Where this is not possible, patients may wait away from the dialysis unit until they receive specific instructions from the unit staff

2. The screening area should have adequate space to implement social distancing between patients and accompanying persons while waiting for dialysis staff. In screening area, every patient should be asked about:

- Symptoms suspected of COVID-19 as above.
- History of contact with a diagnosed case of COVID 19
- History of contact with person who has had recent travel to foreign country or from high COVID-19 prevalence area within our country as notified by the Central and state governments respectively.

3. Patients with symptoms of a respiratory infection should put on a facemask before entering screening area and keep it on until they leave the dialysis unit. Dialysis unit staff should make sure an adequate stock of masks is available in screening area to provide to the patients and accompanying person if necessary.

c. Inside Dialysis Unit

1. Suspected or positive COVID-19 patients should properly wear disposable three-layer surgical mask throughout dialysis duration

2. Patients should wash hands with soap and water for at least 20 s, using proper method of hand washing. If soap and water are not readily available, a hand sanitizer containing at least 60% alcohol can be used

3. Patients should follow cough etiquettes, like coughing or sneezing using the inside of the elbow or using tissue paper. This may be displayed in pictures which are available from the CDC website https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/dialysis.html

4. Patients should throw used tissues in the trash. The unit should ensure the availability of plastic lined trash cans appropriately labeled for disposing of used tissues. The trash cans should be foot operated ideally to prevent hand contact with infective material.

II. For Dialysis Staff

a. Screening Area

1. The unit staff should make sure an adequate stock of masks and sanitizers are available in screening area to provide to the patients and accompanying person if necessary.

b. During Dialysis

1. We suggest to ensure that a patient and staff in a unit does not become the source of an outbreak

2. Each dialysis chair/bed should have disposable tissues and waste disposal bins to ensure adherence to hand and respiratory hygiene, and cough etiquette and appropriate alcohol-based hand sanitizer within reach of patients and staff

3. Dialysis personnel, attendants and caregivers should also wear a three-layer surgical facemask while they are inside dialysis unit

4. Ideally all patients with suspected or positive COVID-19 be dialyzed in isolation. The isolation ideally be in a separate room with a closed door, but may not be possible in all units. The next most suitable option is the use of a separate shift, preferably the last of the day for dialyzing all such patients. This offers the advantage of avoiding long waiting periods or the need for extensive additional disinfection in between shifts. The next suitable option is to physically separate areas for proven positive and suspected cases. Where this is also not possible, we suggest that the positive or suspected patient may be dialyzed at a row end within the unit ensuring a separation from all other patients by at least 2 meters

5. Staff caring for suspected or proved cases should not look after other patients during the same shift

6. Dialysis staff should use of all personal protective equipment (PPE) for proven or strongly suspected patients of COVID-19. We suggest that isolation gowns should be worn over or instead of the cover gown (i.e., laboratory coat, gown, or apron with incorporate sleeves) that is normally worn by hemodialysis personnel. If there are shortages of gowns, they should be prioritized for initiating and terminating dialysis treatment, manipulating access needles or catheters, helping the patient into and out of the station, and cleaning and disinfection of patient care equipment and the dialysis station. We suggest that sleeved plastic aprons be used in addition to and not in place of the PPE recommended above

7. We suggest separating equipment like stethoscopes, thermometers, Oxygen saturation
probes, and blood pressure cuffs between patients with appropriate cleaning and disinfection in between shifts
8. Stethoscope diaphragms and tubing may be cleaned with an alcohol-based disinfectant including hand rubs in between patients. As most NIBP sphygmomanometer cuffs are now made of rexine they may also be cleaned by alcohol or preferably hypochlorite-based solutions however the individual manufacturers manuals may be referred to
9. Staff using PPE should be careful for following issues:
   • While using PPE, they will not be able to use wash room so prepare accordingly
   • After wearing eye shield, moisture appears after some time and visibility may become an issue. Therefore, machine preparation can be done in non-infected area before shifting to near the patient
   • If dialysis is to be done bed-side in the hospital, portable RO should be properly disinfected with hypochlorite solution between use of two patients.

Disinfection and Disposal Practices in Dialysis Unit
• We recommend that that bed linen be changed between shifts and used linen and gowns be placed in a dedicated container for waste or linen before leaving the dialysis station. Disposable gowns should be discarded after use. Cloth gowns should be soaked in a 1% hypochlorite solution for 20 min before sluicing and then be transported for laundring after each use
• We recommend that inside unit, clean and disinfect frequently touched surfaces at least thrice daily and after every shift. This includes bedside tables and lockers, dialysis machines, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks
• We recommend that solutions for disinfection be composed either of hypochlorite, alcohol, formaldehyde, or glutaraldehyde for disinfection of surfaces in accordance with the manufacturer’s instructions. A more complete list of all disinfectants approved by the CDC is available on the CDC website https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-Recommendations.html. Almost all common disinfectant solutions are effective in killing the virus on surfaces, the key is effective and frequent cleaning.
   • Bleach solution
     • Mix 1 Lof Medichlor with 9 L of water. This solution can be used for upto 24 h after which it should be discarded and a fresh solution prepared
   • As an alternative 10 g of household bleaching powder can be dissolved in a liter of water and used for a period of 24 h.
   • Alcohol-based solutions
     • Ensure solution has at least 60% alcohol. Appropriate commercially available solutions include Aerodosin a mixture of isopropanol, glutaraldehyde, and ethanol or lysoformin a mixture of formaldehyde and glutaraldehyde
     • Wear unsterile but clean disposable gloves when cleaning and disinfecting surfaces. Gloves should be discarded after each cleaning. If reusable gloves are used, those gloves should be dedicated for cleaning and disinfection of surfaces for COVID-19 and should not be used for other purposes. Clean hands by above method immediately after gloves are removed
     • For soft (porous) surfaces such as carpeted floor, rugs, and drapes, remove visible contamination if present and clean with appropriate cleaners indicated for use on these surfaces. After cleaning launder items as appropriate in accordance with the manufacturer’s instructions. If possible, launder items using the warmest appropriate water setting for the items and dry items completely
     • Wear disposable gloves when handling dirty laundry from an ill person and then discard after each use. Do not shake dirty laundry. This will minimize the possibility of dispersing virus through the air
     • Clean and disinfect clothes buckets or drums according to guidance above for surfaces. If possible, consider placing a bag liner that is either disposable (can be thrown away) or can be laundered.

Dialysis Patient with Acute Kidney Injury
A small proportion of patients (~5%) of COVID develops AKI. The disease is usually mild but a small number may require RRT. In addition, even smaller proportion of patients with secondary bacterial infection will have septic shock, drug nephrotoxicity, or worsening of existing CKD severe enough to require RRT[6,7]
• We suggest that all modalities of RRT may be used for patients with AKI depending on their clinical status
• Patient admitted in other ward of the hospital with AKI should be preferably given bedside dialysis rather than shifting patient in main dialysis unit
• In such situation portable reverse osmosis water in a tank will serve the purpose for the dialysis
• If more dialysis is expected in selected area, dialysis machine may be left in the same area for future dialysis.

Continuous Renal Replacement Therapy (CRRT)
• CRRT machines are free standing and can function
Personal protective equipment must be used while dialyzing, with filters. However, as the life of such masks is approximately 6–8 h and they can be uncomfortable over a long term and are also in short supply they should be prioritized for aerosol generating procedures, namely intubation, open suction, and bronchoscopy. Surgical triple layer masks and cloth masks can be used as alternatives for all other procedures

- Surgical gloves.

The correct method of donning and doffing personal protective equipment’s (PPE) can be viewed on YouTube at https://www.youtube.com/watch?v=kKz_yNGsNhc. However, it is always better to give hand on training of donning and doffing to staff who is going to handle suspected or positive patients.

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**Conflicts of interest**

There are no conflicts of interest.

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COVID-19 pandemic poses challenges to both public and private sector providers of renal replacement therapy (RRT). Many hospitals are converted into COVID dedicated hospitals, and non-COVID patients requiring hemodialysis (HD) are facing challenges to get spot for maintenance HD. Dialysis units are limited with the resource of dialysis materials and isolation room for COVID patients due to lockdown. SARS CoV-2 positive patients developing acute kidney injury (AKI) also requires dialysis. Peritoneal dialysis (PD) is emerging as a safer alternative to patients requiring chronic dialysis as well as acute dialysis in the intensive care unit (ICU) setting. PD patients remain isolated at home during the pandemic, avoiding exposure to in-center dialysis. Although, there are no significant data from the world, but the following guidelines can be adhered to manage SARS CoV-2 infections in PD patients.

Role of Acute PD in AKI in COVID 19 Patients

As of now, experience from China, Italy, and the USA, it is known that kidney injury is the second most common complication, only after lung injury, in COVID 19 infected patients. A total of 5% of those admitted in the ICU may require some form of renal replacement therapy. According to experienced centers, continuous RRT is the preferred modality. However, there are several centers in the US and Europe, who have used PD in AKI related to COVID 19. In cases, where adequate ventilation may be an issue and PD fluid in the abdominal cavity may be of concern, small, frequent dwells may avoid compromise in ventilation without affecting the adequacy. For hypercatabolic states, tidal or high-volume PD can be advised, and due care should be taken for diet supplementation.

We suggest that acute PD can be used as a modality of RRT for COVID induce AKI in case of unavailability of CRRT and HD.

Chronic PD and COVID 19

The issues which might need to be addressed include—isolation, precautions for care provider, disposal of spent dialysate, managing supplies, OPD visits, management of PD-related peritonitis, and treatment of SARS CoV-2 infection.

Guideline for patients

We suggest that chronic PD should be continued in a room dedicated to PD procedure as before the pandemic.

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Isolation is the only proven means toward prevention and PD patients are not different. In this respect, PD patients are at advantage as they do not need to travel for in-center dialysis.[2,3] They can be easily isolated at home with regular PD going on as before. They are well-trained to follow all the precautions suggested to prevent COVID 19, like hand washing (6-steps), use of mask, use of sterilillium, avoiding hospital visits, etc., during break-in period in the beginning of PD.

Guidance for caregivers

Many of the PD patients need support from care providers, mostly a family member but occasionally PD nurse assisting them in doing the procedure. It is better to avoid having a nurse who is staying elsewhere. Therefore, a family member should be well trained to do the procedure to avoid anyone with higher exposure coming in contact to PD patients. Moreover, it is important to emphasize that any suspected or infected person should not be caring for PD patients. All caregivers should follow the basic precautions of use of mask, gloves, disinfectants, and other protective devices.

We suggest using PPE for all care givers if the patient is positive for SARS-CoV-2 infection. In case of COVID negative status, family members should preferably do the procedure if the patients cannot do the procedure themself.

Guidance for PD effluent disposal

Since, there is no evidence as of now, whether the virus is excreted in the PD effluent or not, it should be considered infected and should be disposed of as is done in patients with human immunodeficiency virus infection.

This includes adequate personal protective equipment (PPE) including gloves, mask, eye shield or other, as per anticipated exposure, while draining into the toilet and avoiding splash. Household bleach which is an effective disinfectant, may also work for COVID 19, can be used in dilution of 1:10 in the toilet and left for 5 min before flushing or by adding 500 mg/L chlorine containing solution for 1 h before pouring into the toilet.[4] Used PD bags and tubings should be placed in a plastic bag, sealed, and put in another bag (double bagged) before being discarded. PD effluent of suspected or proven COVID 19 infection, when sent for analysis, should be adequately labeled, for ‘careful’ handling by the laboratory.

Guidance for the supplies

Supplies are an important issue faced with many of our patients because of long “lockdown”.[2,5] All attempts must be made to arrange for the supplies. Bags can be shared among patients, who have larger supplies. Few patients have cut down their number of exchanges by one per day, which should better be avoided but may be the only option at times of crisis.

We suggest PD fluid and other accessories required for PD should be supplied without any interruption.

Guidance for peritoneal equilibration test and other investigations

Routine OPD visits should be avoided and “telemedicine” can be utilized for care of PD patients.[3] Only emergency services should be promoted. Non-urgent procedures like PET, clearance studies, elective surgeries, etc., should be postponed. There is no data to stop angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) in those already having it for the concern of infection.

We suggest that patients should continue all other medications as before including ACEI or ARB. PET and clearance tests should be avoided during pandemic.

Precautionary measures for PD patients wanting to visit hospital for a checkup

All patients who need to come to the hospital for a visit should be screened by telephone or text messaging regarding the presence of any symptoms of COVID 19 (fever or any signs of acute respiratory infection, such as shortness of breath, cough or sore throat) or, has anyone in their family got COVID-related symptoms, any history of being in contact with someone who has developed COVID 19 infection in the last 2 weeks, or any travel history in the last 14 days.[4] If a patient has symptoms or signs suggestive of COVID 19 infection and needs to be seen by the doctor or nurse, the patient should be seen with appropriate infection control procedures.

PD peritonitis can also be managed via “video consultation”. Prescriptions can be sent as an attachment and PD fluid testing can also be done by “home collections” where available.

We suggest that patient should start intraperitoneal antibiotics for PD-related peritonitis as they have been trained for that before start of PD. PD effluent culture should be sent with all precautions and label to the PD effluent. Patients should only be admitted in case of refractory peritonitis or, any other indications of Tenckhoff catheter removal is emerged.

Treatment of COVID 19 infection in PD patients

The treatment remains the same as in any other COVID-19 patients which includes supportive treatment along with local practice of use of antiviral or other experimental therapies.[9] The use of HCQ is also debatable and should be guided by local health guidelines. Many of these medicines may require dose modification as applicable for PD patients. Attempts should be made to preserve residual renal function and to avoid offending drugs like pain killers. The outcome of PD patients...
infected with COVID 19 infection is not known and data are awaited. Severe or critically severe cases requiring life support due to multiple organ failure can be temporarily transferred to automated peritoneal dialysis or even extracorporeal therapies.

As new data are emerging, one should be vigilant for better evidence in the coming days, regarding managing PD patients with or at risk of COVID-19 patients.

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There are no conflicts of interest.

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COVID 19 and Hemodialysis Anxiety

Dear Sir,

The initial outbreak of coronavirus disease (COVID 19) was started in Wuhan, China, in December 2019 but rapidly spread worldwide to become pandemic causing grave threat to human race. Currently, number of COVID 19 cases has risen significantly in the United States, most of the Europe, Middle East, Asia, and Australia.[1]

The critical presentations leading to fatality have been more frequently associated with preexisting comorbidities like diabetes mellitus, cardiovascular disease, elderly population, and probably due to fragile immune system.[1] Large number of chronic kidney disease (CKD) patients, already having these comorbidities, are more vulnerable for COVID 19 complications. As a pandemic response, most of people have been advised to “stay at home” by doing nationwide lockdown in many countries as per infection control policy, but CKD patients on in-center maintenance hemodialysis (MHD) are bound to come to hospitals for their treatment.[2,3] In addition to this, MHD patients are readily distinguishable by some unique features which make them at high risk in the current COVID 19 pandemic. These characteristics include potential close contact for significant duration to other patients, nurses, and dialysis staffs during dialysis; CKD patients undergo MHD treatments in a much-closed space putting them at high risk for exposure to COVID 19. Taking all these considerations into account, patients on MHD are be considered at risk population for COVID 19 pandemic.[3,4]

During this pandemic of COVID 19, fear and panic wave is advancing worldwide ahead of the virus, which is mostly being induced by misleading and biased information through unfiltered social networks. This has provoked significant stigma of disease and started discrimination amongst people with its ill effects on disease containment strategies.[1,2] Amidst these uncertainties, health-care workers are not only going through tremendous physical stress due to intense work load but also developed mental exhaustion due to loss of few of their patients and their workmates. Additionally, their continuous functionality in infectious environment along with shortage of personal protective equipment (PPE) initiated panics among them as well.[2,5]

CKD patients on MHD and their caregivers are already suffering from depression and anxiety, but mostly underestimated and neglected. This unrecognized issue may lead to poor quality of life among them and never been optimally treated.[6] On top of this, the current turmoil of fear and apprehension launched by COVID 19 may lead to fuelling of more psychological disturbances among the CKD patients and their caregivers leading to hospital-related anxiety, which may be more hazardous for these fragile patient populations. Interestingly during this pandemic, medical professionals have been more inclined to emphasize on the biological aspects of disease transmission and prevention for dialysis unit functionality but can misjudge the importance of impaired mental sphere of MHD patients and their caregivers.[6,7] In the ongoing unrest, whether patient is presenting with COVID 19 symptoms or non-COVID illness may be misleading many times in patients on MHD and they are being diverted for screening to COVID 19 designated facilities, which may further compromise already weaken health-care systems, especially in developing countries like India with its limited resources.[2]

Fear may have led to underestimation of non-COVID etiologies of fever and respiratory symptoms, which could lead to delay in management of other treatable ailments. Media reports from India say that many dialysis facilities are being shut down for few days, when a patient on MHD is affected with COVID 19, and the exposed staffs being quarantined, without making alternative arrangements, which is creating access to dialysis more difficult. Additionally, due to fear, many patients in areas with disease hotspots are denied of life-saving dialysis in the absence of laboratory report.[2] After completing quarantine period, many dialysis staff and doctors have anxiety to resume duties due to shortage of PPE in many hospital settings. Besides these, as dialysis workforces are distinctly skillful and specialized, it is difficult to substitute them in this pandemic situation.[5] Ultimately, this anxiety has initiated more frustration for these frail CKD patients and their caregivers including nephrologists. This collateral damage triggered by COVID 19 pandemic is myriad and mostly unnoticed, though actually may give rise more morbidity and mortality than COVID 19 itself for which we need more realization and vigilance.[2]

In the COVID 19 context, important hurdles for hemodialysis population include disruption of supply chain of dialysis consumables and imported equipment, logistical issues to reach hemodialysis center after suspension of public transport,[2] and added costs for PPE and COVID 19 test passed on to patients, which increases dialysis cost with reimbursement stress. Another major obstacle is shortfall of dedicated area for COVID 19 suspect and positive patients in many hospitals which cannot be resolved out immediately. These aftermaths of pandemic are still not addressed for which we have to take necessary steps at the earliest.

In the present scenario, many documents came up with preventive recommendations in dialysis population and
for health-care workers safety,[3,4] but reports on the actual magnitude of fear and anxiety along with its impact on CKD patients and dialysis staff are immensely needed. In our opinion, we can overcome this common enemy with collective efforts.

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Renal Transplant Guidelines with Reference to COVID-19 Infection

Abstract
Development of COVID-19 pandemic has affected organ transplant activity significantly. To start with, government of India had advised stoppage of “elective” surgeries so as to cope with resources and manpower for COVID-19 patients. As majority of hospitals are having both COVID and Non-COVID patients, there is obvious fear of cross-infection. Also, transplant patients being immunocompromised, there is higher risk of acquiring COVID-19 infection along with atypical presentation and unpredicted course of the disease. Result was that across India, elective living related kidney transplant came to a halt. Cadaver renal transplant, being emergency in nature still done, though very few. With passing time, once it became clear that pandemic is not going to be controlled sooner, need has been felt to restart renal transplant activity. Keeping various issues in mind in relation to elective living related renal transplant and emergency deceased donor renal transplant, these guidelines have been framed to help transplant professionals for restarting renal transplant program again in the country, while keeping both health care workers and patient safe.

Keywords: COVID-19, guidelines, renal transplant

These guidelines have been prepared by COVID-19 Working Group of Indian Society of Nephrology and endorsed by the Indian Society of Organ Transplantation (ISOT). In view of the rapidly changing scenario of COVID-19 infection, these guidelines may be revised/updated from time to time.

Organ transplant recipients are at a risk for more severe COVID-19 if they get SARS CoV-2 viral infection. Further, there is a potential risk of infection transmission from the donor to recipient through organ transplantation. Also, there are issues in recipient and donor selection for transplant. In view of these issues’ organ transplants at the time of COVID-19 pandemic should be undertaken with caution and should be done only at the center where facilities of management of COVID-19 patients are available.
1. The pre, peri, and posttransplant areas, including the operation theaters need to be specifically ear-marked for this purpose
2. Staff involved in the care of transplant patients must not be involved in the care of other patients
3. There has to be adequate availability of personal protective equipment (PPE) for the care of these patients
4. The center should not be the one ear-marked for the treatment of COVID-19 patients and needs to have protocols for patient movement around the hospital to prevent the nosocomial acquisition of COVID.

Deceased Donors Transplants
Following individuals, having any of the following criteria, who are potential deceased donor should NOT be accepted as deceased donors:

a. Epidemiological criteria –
• International travel in the last 14 days before the onset of current event leading to brain stem death
• Contact in last 14 days before the onset of current event leading to brain stem death with a confirmed case of COVID-19 or a health care worker with direct patient contact
b. Clinical criteria –
• Where the cause of death was due to unexplained respiratory failure
• Where there was a history of fever or acute respiratory infection (e.g., shortness of breath, cough, and sore throat) with or without
without fever.
• Severe bilateral community-acquired pneumonia in the absence of any other cause.
c. Laboratory criteria -
• Confirmed COVID-19 positive case or test found positive while donor work-up is being done.

Routine testing of deceased donors
Routine COVID-19 (SARS-CoV-2) viral testing should be undertaken in all potential deceased donors within 72 h prior to donation, both for assessment of donor fitness as well as for improving the safety of staff involved in transplantation

Even though the potential deceased donor is fit to donate organs, every hospital and organ transplant system must balance between the care of other COVID-19 positive patients in their health care setting against the organ transplant vis-a-vis availability of resources for safely conducting the organ transplant.

Living related Transplants
The living donor transplant program may be temporarily suspended in line with the Ministry of Health and Family Welfare (MoHFW)’s advisory for Hospitals and Medical Institutions dated 3rd March 2020, accessible at https://www.mohfw.gov.in/pdf/AdvisoryforHospitalsandMedicalInstitutions.pdf

However, if transplant is being done in view of the emergency medical need of recipient, following individuals, who are living donor should NOT be accepted as donors:

a. Epidemiological criteria –
• International travel in the last 14 days
• Contact in last 14 days with a confirmed case of COVID-19 or a health care worker with direct patient contact

b. Clinical criteria –
• History of fever or acute respiratory infection (e.g. shortness of breath, cough, sore throat) with or without fever

c. Laboratory criteria -
• Confirmed COVID-19 positive or test found positive while donor work-up is being done.

Reverse transcription-polymerase chain reaction (RT-PCR) test of potential donors should be undertaken as suggested for deceased donors

Emergency life-saving Transplantation
In case a transplant is to be done due to the emergency need of the recipient, it should be performed with the appropriate assessment of COVID-19 infection in the recipient. Further, appropriate counseling of both the donor and recipient as well as their families should be done, and a high-risk informed consent should be taken before proceeding with the transplant.

Transplantation Recipients
Similar to the general population, transplant recipients should also strictly follow the travel advisories issued by the various ministries of the Government of India from time to time. They should take extra precaution as they have a risk of developing severe COVID-19 disease, if they acquire SARS CoV-2 viral infection.

Transplant Recipients Returning from Abroad
All transplant recipients who have been exposed to a confirmed or suspected COVID-19 patient within the last 14 days or who have returned from nations with COVID-19 outbreaks should undergo quarantine and isolation for 14 days and should be tested for SARS CoV-2 infection.

If any transplant recipient has fever, cough, or breathing difficulty, they should immediately call their respective transplant centers. All transplant centers must have guidelines in place specifying which patients need testing and inpatient management and which patients can stay at home with close follow-up with various means like mobile and email etc.

If they are advised to visit the hospital, they should wear a mask while coming to hospital premises. In case of a medical emergency like difficulty in breathing, they should report to the nearest emergency department.

Treatment and modification of immunosuppression
There are two issues of management of organ transplant patients with COVID-19

a. Management of COVID-19 in the transplant patient
   There is a scarcity of data and consensus on effective treatments of COVID-19 as such and more so in transplant patients. Few centers have tried antivirals, hydroxychloroquine, and macrolides in COVID-19 patients with variable results. However, as of now, there is no treatment approved by the Central Drugs Standard Control Organization (CDSCO) or the Foods and Drug Administration (FDA) for COVID-19

b. Handling of immunosuppressive medicines with COVID-19
   There is no consensus regarding modification in the immunosuppressive regimen of transplant recipients with COVID-19. The dose adjustment has to balance the infection control and the organ rejection. However, there is an overall agreement of stopping antimetabolite drugs and decrease calcineurin inhibitors by 50%. Steroids should be continued on same doses. (Massachusetts General Hospital COVID-19 Treatment Guidance).
Posttransplant follows up Measures

Transplant patients are at risk for severe COVID 19 if they acquire infection due to their immunosuppressed state. They may not manifest symptoms like the general population. Fever may be absent as reported from a study from China. Transplant units are advised to consider ways to limit hospital attendance for patients, such as:
1. Rescheduling nonurgent out-patient appointments
2. Virtual or telemedicine or telephonic appointments
3. Home delivery of immunosuppression if feasible.

Patients with stable graft function and adequate drug supply can avoid routine follow-up visits to transplant hospitals.

Tissue Transplantation

At present, there is no evidence to suggest the transplant of coronaviruses by blood transfusion.

Tissue and Eye Donation Criteria

The deferral will be based upon infection status in the last 28 days before donation:
• Positive test for COVID-19
• Symptoms consistent with COVID-19 infection (e.g., unexplained fever, cough, shortness of breath) in a patient with suspected COVID-19 infection
• Donor defined as a person under investigation (PUI)
• Fever with severe acute lower respiratory illness (e.g., pneumonia, ARDS).

Additionally, the deferral will be based upon exposure in the last 28 days before donation:
• Close contact with a person who has confirmed COVID-19
• Close contact with a person under investigation (PUI) for COVID-19
• International travel.

Personnel Precautions working in the program

The health and safety of all the health care workers in the transplant program is of paramount importance. Transplanting hospitals are advised not to expose any of their staff if there is even the slightest risk of virus transmission from both epidemiological and clinical criteria.

It is likely that this pandemic may require the current resources to be utilized elsewhere, hence there is even more reason to practice caution when deciding on proceeding with donation and transplantation. It is with this in mind that all elective live living kidney and liver transplant should be postponed.

General principles for handling SARS CoV-2 infection in a transplant center

1. Personnel should follow all hospital-based protocols for the isolation and management of COVID-19 patients
2. Any questions or concerns about the infectious status of a potential donor should be referred to your medical director/organ sharing body for further guidance
3. If a donor is being ruled-out due to hospital considerations, local or national health authorities be sure to record the information. It is important that this information must be documented clearly and accurately. Documentation should include transmittable disease status, COVID-19 testing status/high-risk suspicion and/or individual organ suitability
4. Screening questions should reflect updated COVID-19 national guidelines.

Please refer to below links for more information:
• Coronavirus (SARS-CoV-2) causing COVID-19: Information for donation and transplant professionals Version 1 dated 18-3-2020 – BY Donate Life & The Transplant Society of Australia & New Zealand https://tts.org/23-tid/tid-news/657-tid-update-and-guidance-on-2019-novel-corona-virus-2019-ncov-for-transplant-id-clinicians
• https://www.mohfw.gov.in/pdf/AdvisoryforHospitalsandMedicalInstitutions.pdf
• https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19#fastfacts
• https://www.gaeba.org/2020/alert-corona-virus-2019-ncov-and-ocular-tissue-donation/
• Guidelines for Liver Transplantation and COVID-19 Infection, as received from the President, Liver Transplant Society of India (LTSI) via official correspondence on 23-03-2020.

Disclaimer

The current outbreak is unpredictable. If widespread community-transmission occurs, health care infrastructure and capacity issues may have a further impact on donation and transplantation. These recommendations may require regular updation to account for the changing epidemiology and new information regarding the treatment and testing. All transplant units must be aware of national and local guidance for managing patients with COVID-19.

No suit or legal proceedings shall lie against any person for anything done or intended to be done in good faith under this suggestions/advisory unless proved otherwise.
Anti-corona Drugs: Current Scenario

In late December 2019, an outbreak of an emerging disease (coronavirus disease of 2019 [COVID-19]) due to a novel coronavirus (named SARS-CoV-2 latter) started in Wuhan, China, and rapidly spread in China and outside. The World Health Organization (WHO) declared the epidemic of COVID-19 as a pandemic on March 12, 2020. The overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70–79 years and 14.8% in those aged >80 years.

The number of people diagnosed with COVID-19 worldwide crossed the one and half million mark on April 10, 2020; the case fatality rate across 204 countries and territories was 5.2%.[1]

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2.

Infected patients should receive supportive care to help alleviate symptoms. Vital organ function should be supported in severe cases. There is little empirical evidence to guide the management of COVID-19. However, with 80,000 new cases being confirmed daily and the rate still increasing, clinicians taking care of patients with COVID-19 need guidance now. The suggestions mentioned here are based on scarce direct evidence, indirect evidence, and clinical observations. The goal is to improve outcomes and facilitate research by standardizing care. The suggestions provided in this document should never be considered mandates, as no suggestion can incorporate all potential clinical circumstances. The suggestions are interim guidance and will be reevaluated as evidence accumulates.

Numerous collaborative efforts to discover and evaluate the effectiveness of antivirals (e.g., remdesivir), immunotherapies (e.g., hydroxychloroquine, sarilumab), monoclonal antibodies, and vaccines have rapidly emerged. The enthusiasm to try new therapies during outbreaks must be balanced against ethical and scientific safeguards. Although expert guidance can be sought from local or international societies, patients treated with experimental therapies should be enrolled in a clinical study when possible.

Vaccines

No vaccine is currently available for SARS-CoV-2. Avoidance is the principal method of deterrence. A phase 1 clinical trial is now planned for an experimental vaccine against SARS-CoV-2, mRNA-1273, by Moderna.

Antiviral Therapy

Lopinavir/ritonavir

The guidelines of the Chinese National Health Commission recommend aerosolized inhalation of interferon-β (IFNβ) and lopinavir/ritonavir.[2]

The specific therapeutic value and safety of lopinavir/ritonavir in patients with COVID-19 are under investigation.

In a randomized, controlled, open-label trial of hospitalized adults (n = 199) with confirmed SARS-CoV-2 infection, recruited patients had an oxygen saturation of 94% or less on ambient air or PaO2 of less than 300 mm Hg and were receiving a range of ventilatory support modes (e.g., no support, mechanical ventilation, extracorporeal membrane oxygenation [ECMO]). These patients were randomized to receive ritonavir/lopinavir 400 mg/100 mg PO BID for 14 days added to standard care (n = 99) or standard care alone (n = 100). Results showed that time to clinical improvement did not differ between the two groups (median, 16 days). The mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs. 25%) but did not reach statistical significance. In hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.[3]

An editorial accompanies this study that is informative in regard to the extraordinary circumstances of conducting such a study in the midst of the outbreak.[4]

The WHO has not taken a position on the use of lopinavir-ritonavir in COVID-19 but its SOLIDARITY trial includes a lopinavir ritonavir arm. The CDC states that “lopinavir-ritonavir did not show promise for the treatment of hospitalized COVID-19 patients with pneumonia in a recent clinical trial in China. This trial was underpowered...” The FDA has not taken a position on the use of lopinavir-ritonavir in COVID-19. The Surviving Sepsis Campaign made a weak recommendation against the routine use of lopinavir-ritonavir.[5]

Remdesivir

The broad-spectrum antiviral agent remdesivir (GS-5734; Gilead Sciences) is a nucleotide analog produrg. Several phases 3 clinical trials are underway for testing remdesivir for use in COVID-19 in the United States, South Korea, and China. They were deemed to be the most promising candidate drug by experts.

An in vitro study showed that the antiviral activity of remdesivir plus IFNβ was superior to that of lopinavir/ritonavir (LPV/RTV; Kaletra, Aluvia; AbbVie Corporation). Prophylactic and therapeutic remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology in mice, whereas LPV/RTV-IFNβ slightly reduced viral loads without affecting other disease parameters. Therapeutic LPV/RTV-IFNβ improved

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pulmonary function but did not reduce virus replication or severe lung pathology.\[6\]

Successful treatment with remdesivir has been reported in a patient with COVID-19; a clinical trial on the efficacy of remdesivir in patients with COVID-19 is currently underway in China (NCT0425266; NCT04257656) and is expected to be completed in April 2020. No peer-reviewed, published safety data are available for SARS-CoV-2. The WHO has not taken a position on the use of remdesivir in COVID-19 but its SOLIDARITY trial includes a remdesivir arm. The CDC has not taken a position on remdesivir but describes options for obtaining it for hospitalized patients with COVID-19 and pneumonia. The FDA reports that it has been working with the maker of remdesivir to find multiple pathways to study the drug under the FDA's investigational new drug requirements and to provide the drug to patients under emergency use. The Surviving Sepsis Campaign made no recommendation for or against remdesivir due to insufficient evidence.\[5\]

**Chloroquine and hydroxychloroquine**

Chloroquine phosphate has been shown to have some efficacy against COVID-19-associated pneumonia in multicenter clinical trials conducted in China.\[7\]

According to a consensus statement from a multicenter collaboration group in China, chloroquine phosphate 500-mg twice daily in tablet form for 10 days may be considered in patients with COVID-19 pneumonia.\[8\]

Wang et al.\[9\] reported that chloroquine effectively inhibits SARS-CoV-2 in vitro.

Hydroxychloroquine and chloroquine have been shown to have in vitro activity against SARS-CoV-2, with hydroxychloroquine being more potent.\[9,10\] Clinical trials, however, provide an inconsistent message. Small controlled clinical trials from more than 10 hospitals in China reportedly indicate that chloroquine is superior to controls in preventing pneumonia, improving lung imaging findings, hastening conversion to a virus-negative state, and shortening the duration of disease.\[11\] However, two of the trials are now publicly available, and they have important limitations: in a negative trial, both arms included patients who had undergone treatment with anti-viral drugs\[12\] and, in a positive trial, the arms of the trial had important baseline differences.\[13\] A small controlled trial from France reported that hydroxychloroquine hastens conversion to a virus-negative state, but important limitations included a lack of patients with severe illness, lack of blinding, no randomization, and loss to follow-up.\[14\] The results are notable for a shift toward treatment with hydroxychloroquine or chloroquine as the severity of COVID-19 increased, indicating that the perceived balance of potential benefits to harms changed as the severity of illness increased.

The WHO has warned against the use of medications that have not been proven in an RCT; its SOLIDARITY trial includes a chloroquine arm. The CDC says, “There are no currently available data from RCTs to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection.” The US FDA stated that there is insufficient evidence to support treatment of COVID-19 with hydroxychloroquine or chloroquine, but issued an emergency-use authorization to allow both donated drugs “to be distributed and prescribed by doctors to patients with COVID-19, as appropriate, when a clinical trial is not available or feasible.” The Surviving Sepsis Campaign made no recommendation for or against hydroxychloroquine or chloroquine due to insufficient evidence.\[5\]

The National Taskforce for COVID-19 from India recommended the use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection for:
1. Asymptomatic healthcare workers having direct contact with suspected or confirmed cases of COVID-19
2. Asymptomatic family contacts of confirmed cases.

This recommendation is subject to the following conditions:
1. Hydroxychloroquine is found to be effective against coronavirus in laboratory studies and in-vivo studies. Currently, there is no direct evidence about its role in prophylaxis. The recommendation for the use of hydroxychloroquine as a prophylactic agent against SARS-CoV-2 infection is based on empirical evidence, as well as risk-benefit consideration, and its safety profile.
2. Dose:
   a. Asymptomatic healthcare workers: 400 mg per week for 8 weeks
   b. Asymptomatic family contacts of confirmed cases: 400 mg per week for 4 weeks.
3. The drug is not recommended for children under 15 years of age
4. The drug is contraindicated in persons with significant hepatic or renal dysfunction and those with known hypersensitivity to the 4-aminoquinoline compound.

**Glucocorticoids**

Patients with COVID-19 have elevated levels of pro-inflammatory cytokines and other inflammatory biomarkers, leading some clinicians to postulate that systemic corticosteroid therapy may be beneficial. In a retrospective study of patients with SARS-CoV and sepsis, steroids, at a mean daily dose of 105.3 _ 86.1 mg in 147 of 249 noncritical patients (59.0%), reduced mortality rate and shortened duration of hospitalization, whereas 121 of 152 critical patients (79.6%) received corticosteroids at a mean daily dose of 133.5 _ 102.3 mg, and 25 died.\[15\]

A subsequent retrospective, observational study of 309 patients with MERS showed that those who received...
high-dose steroids were more likely to require mechanical ventilation, vasopressors, and RRT.\textsuperscript{[13]}

A retrospective study of 84 patients with ARDS associated with COVID-19 found lower mortality in those treated with methylprednisolone, but the findings are limited by the observational design of the study, small sample size, and possible confounders.\textsuperscript{[16]}

In a meta-analysis of corticosteroid use in patients with SARS, four studies provided conclusive evidence of harm (psychosis, diabetes, avascular necrosis, and delayed viral clearance).\textsuperscript{[17]}

Therefore, the use of steroids is controversial and not recommended by the World Health Organization because of potential inhibition of viral clearance and prolongation of the duration of viremia.\textsuperscript{[18]}

The WHO says that clinicians should “not routinely give systemic corticosteroids for the treatment of viral pneumonia outside clinical trials.” The CDC says “corticosteroids should be avoided unless indicated for other reasons, such as management of chronic obstructive pulmonary disease exacerbation or septic shock.” The FDA has not taken a position on the use of systemic corticosteroids in COVID-19. The Surviving Sepsis Campaign made a weak recommendation against systemic corticosteroids in mechanically ventilated COVID-19 patients without ARDS, but a weak recommendation for systemic corticosteroids in mechanically ventilated COVID-19 patients with ARDS.\textsuperscript{[5]}

**Convalescent plasma**

Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. This has been noted in Ebola and Middle East respiratory syndrome viral infections.\textsuperscript{[19,20]}

One possible explanation for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viremia.

Preliminary clinical studies in China have shown that early application of convalescent plasma in patients with COVID-19 could accelerate clinical recovery.\textsuperscript{[21]}

Findings from a preliminary study of five severely ill patients with COVID-19 who were treated in the Shenzhen Third People’s Hospital, China, using plasma from recovered individuals.\textsuperscript{[22]} All patients had severe respiratory failure and were receiving mechanical ventilation; one needed ECMO and two had bacterial and/or fungal pneumonia. Four patients without coexisting diseases received convalescent plasma around hospital day 20, and a patient with hypertension and mitral valve insufficiency received the plasma transfusion on day 10. The donor plasma had demonstrable IgG and IgM anti-SARS-CoV-19 antibodies and neutralized the virus in vitro cultures.

Although these patients continued to receive antiviral treatment primarily with lopinavir/ritonavir and IFN, the use of convalescent plasma may have contributed to their recovery because the clinical status of all patients had improvement approximately 1 week after transfusion, as evidenced by normalization of body temperature as well as improvements in SOFA scores and PAO2/FIO2 ratio. In addition, the patients’ neutralizing antibody titers increased, and respiratory samples tested negative for SARS-CoV-2 between 1 and 12 days after transfusion. Even though the cases in this report by Shen et al. are compelling and well-studied, this investigation has important limitations that are characteristic of other “anecdotal” case series. The intervention, administration of convalescent plasma, was not evaluated in a randomized clinical trial, and the outcomes in the treatment group were not compared with outcomes in a control group of patients who did not receive the intervention. Therefore, it is not possible to determine the true clinical effect of this intervention or whether patients might have recovered without this therapy. In addition, patients received numerous other therapies (including antiviral agents and steroids), making it impossible to disentangle the specific contribution of convalescent plasma to the clinical course or outcomes. Moreover, convalescent plasma was administered up to 3 weeks after hospital admission, and it is unclear whether this timing is optimal or if earlier administration might have been associated with different clinical outcomes. Despite these limitations, the study does provide some evidence to support the possibility of evaluating this well-known therapy in more rigorous investigations involving patients with COVID-19 and severe illness. No adverse events were reported among patients receiving convalescent plasma.

Despite the potential utility of passive antibody treatments, there have been few concerted efforts to use them as initial therapies against emerging and pandemic infectious threats. The absence of large trials certainly contributes to the hesitancy to employ this treatment Both academic and industry groups are beginning to investigate the efficacy of passive antibody therapies for COVID-19 infection. Currently two trials, an open-label, nonrandomized clinical trial (NCT04264858) and a multicenter, randomized, and parallel controlled trial (ChiCTR2000029757) on the efficacy of convalescent plasma in patients with COVID-19, is underway in China.

The US FDA has approved the use of plasma from recovered patients to treat people who are critically ill with COVID-19, provided that doctors get approval over the telephone.\textsuperscript{[24]} FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. The guidance also provides recommendations.
to blood establishments on the collection of COVID-19 convalescent plasma.[25]

Monoclonal antibody

A monoclonal antibody against COVID-19 has not yet been developed. Monoclonal antibody directed against the RBD domain of the S Q7 protein of MERS-CoV has been found to have neutralizing activities in plaque assays in vitro.[26]

Tocilizumab

Tocilizumab, a monoclonal antibody against the IL-6 receptor, has achieved encouraging preliminary clinical results. Patients with COVID-19 have elevated levels of the pro-inflammatory cytokine, IL-6, with the most severely ill patients showing the highest levels. Tocilizumab antibody that has proven effective in other IL-6 mediated diseases. It is recommended by China’s National Health Commission for use in COVID-19 patients with elevated IL-6 levels. The WHO, CDC, and FDA have not taken a position on the use of tocilizumab in COVID-19, although the FDA approved an RCT comparing tocilizumab to standard care. The Surviving Sepsis Campaign made no recommendation for or against tocilizumab due to insufficient evidence.[5] The safety and efficacy of tocilizumab in COVID-19 infection are undergoing evaluation by a multicenter randomized controlled trial (ChiCTR2000029765).

Hydroxychloroquine and azithromycin

In an open-label non-randomized French clinical trial confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600 mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. The presence and absence of a virus at Day6-post inclusion was considered the end point. Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination. Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.[14]

Favipiravir

It is a RNA-dependent RNA polymerase inhibitor. It is the Japanese flu drug. Hypothesized to have an antiviral action on SARS-CoV-2 (RNA virus); multiple clinical studies are underway for SARS-CoV-2. A Chinese trail used Favipiravir on 340 patients and showed viral disappearance in 4 days compared to the ones who did not get the drug. However, this trial has been taken off the internet for reasons not specified. No peer-reviewed published efficacy data available for SARS-CoV-2. Preliminary, unpublished trial data suggest a more potent antiviral action with favipiravir compared with lopinavir–ritonavir, but caution is advised in interpreting these results. No peer-reviewed, published safety data available for SARS-CoV-2; preliminary, unpublished trial data suggest fewer adverse events with Favipiravir compared with lopinavir–ritonavir, but caution is advised in interpreting these results.[27]

Secondary hemophagocytic lymphohistiocytosis (sHLH) may be responsible for some of the deaths in adult patients with severe COVID19. Experience of lowvolume plasma exchange (PLEX) with lowdose steroid in the treatment of adult patients with sHLH and acute liver failure caused by dengue virus and other nonviral triggers and how this may be effective in the management of severe COVID19 is dealt in this study from CMC, Vellore. sHLH is poorly understood and without effective treatment. Endothelium of the capillaries of the lungs and kidneys and of liver sinusoids does not express von Willebrand factor (VWF) in health and is where most macrophages are located. Plasma VWF levels are high in sHLH and require clearance by macrophages, which when activated enlarge and likely block the lumen. Current histology studies neither appreciate microcirculatory sludge nor display endothelial–macrophage interactions. The authors hypothesize that lowvolume PLEX and lowdose steroid may reverse sHLH and improve survival in severe COVID19 patients with acute lung injury.[24]

The COVID-19 outbreak is a stark reminder of the ongoing challenge of emerging and reemerging infectious pathogens and the need for constant surveillance, prompt diagnosis, and robust research to understand the basic biology of new organisms and our susceptibilities to them, as well as to develop effective countermeasures.

No drugs or biologics have been proven to be effective for the prevention or treatment of COVID-19. Numerous antiviral agents, immunotherapies, and vaccines are being investigated and developed as potential therapies.

Most patients with COVID-19 in China were given empirical broad-spectrum antibiotics and many, oseltamivir, because laboratory diagnosis of COVID-19 takes time, and distinguishing the disease from other bacterial and viral pneumonias is often difficult. Any empirical antibiotic and anti-influenza therapy should be rapidly de-escalated based on microbiology test results and clinical response.

The trade-off between waiting for evidence before deciding whether to administer a therapy and using a therapy while awaiting evidence isn’t unique; however, it is magnified by the urgency of a pandemic.[29] The tension is probably best
solved by creating evidence during routine patient care, while awaiting clinical trial results.

In conclusion, empirical evidence, particularly randomized trials, are desperately needed to guide therapy. Supportive care remains the mainstay of treatment and social distancing remains an important part of prevention. The suggestions provided in this document will be periodically reevaluated as new evidence emerges and modified accordingly.

When it comes to findings, the COVID-19 train is an express, whereas the rigorous science coach is a local. Until that local arrives at its final destination, it may be wise to label all this research—preprints, peer-reviewed papers—with a black-box warning: “There is some evidence for this now. It will likely turn out to be at least partially wrong.”

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In the current situation, the best way to prevent novel coronavirus disease 2019 (COVID-19) is to avoid exposure to the virus. There is currently no evidence-based treatment and effective vaccine to manage and prevent COVID-19. With the information available now, the main route of spread is between human-to-human, either from a symptomatic affected person or from an asymptomatic carrier, via respiratory droplets or contact. There is still controversy of orofecal and airborne transmission. The limited health infrastructure available and the impending risk of a potentially explosive outbreak necessitates urgent measures to control this pandemic. Social distancing and the following recommendations are found to be most useful to control the pandemic.

The following recommendations apply for all general public as well as to patients with chronic kidney disease, on dialysis and following kidney transplantation.\cite{1,2}

### General Advice
1. Avoid agglomerations and closed crowded spaces
2. Maintain a distance of at least 1-2 meters, especially from persons with respiratory symptoms
3. Stay home if sick or with any respiratory symptoms or even if asymptomatic, if there is a history of contact with a suspected COVID patient
4. Avoid non-essential travel
5. Avoid touching various surfaces unnecessarily.

### Hand Hygiene
1. Wash hands with soap and water for at least 20 seconds, especially after blowing the nose, coughing, sneezing, or being in any public place
2. If the hands are not soiled and/or soap is not available, use a hand sanitizer containing at least 60% alcohol
3. “My 5 moments for hand hygiene” (https://www.who.int/gpsc/5may/background/5moments/en) are a simple, effective guide on how to perform hand hygiene
4. If soap or alcohol-based hand rub is not available, chlorinated water (0.05%) can be used, though repeated use can lead to dermatitis and should be watched out for
5. Refrain from touching your eyes, nose and mouth with unwashed hands
6. Dry your hands with tissue paper (preferably) or with a clean, dry cloth, single-use towel or hand drier as available.

### Respiratory Etiquette
1. Nose and mouth should be covered with a tissue while coughing or sneezing or inside of a flexed elbow should be used. The tissue has to be disposed of in the trash immediately, followed by proper hand hygiene.

### Personal Protective Equipment
Personal protective equipment are alone or combination of multiple consumable used by the healthcare worker (HCW) and other individual and include:\cite{2}
1. Face mask
2. Cap or hood
3. Goggle
4. Face shield
5. Shoe cover
6. Gown
7. Full cover or cover all.

Given the area where the HCW is working and the degree of risk involved, decides what all components of PPE one should use. Three different levels of protection are shown in Table 1. The guidance for the use of PPE in different health setting has been shown in Table 2.

### Table 1: Different levels of protection

| LEVEL-3 PROTECTION | LEVEL-2 PROTECTION | LEVEL-1 PROTECTION |
|--------------------|--------------------|--------------------|
| Branded Coverall (Tyvec, Tynex, etc.) | N95 Mask | N95 mask |
| N95 Goggles | Overall/ Gown | Gown |
| Face shield | Goggles | Goggles (Double) |
| Gloves (Double) | Long shoe cover | Gloves (Double) |
| Long Shoe cover | |

However, as face mask are most commonly used PPE, little more details are usefull.

### Face Mask
Use of face mask and type of face mask is probably the most controversial issue in current pandemic. Its use usually takes into consideration that in which area person is working and what is availability of mask. One should follow the guidelines being provided by the local health authority.\cite{3}
1. Any individual should wear face mask if he has respiratory tract infection, if he cares for those with respiratory symptoms or when entering a healthcare provider’s place
2. There are two broad category of face mask; three-layer surgical mask and N-95 mask
3. A triple-layered surgical mask is sufficient for personal protection in usual situation in healthcare setting
4. N-95 mask is necessary for following situations:
   - If HCW is working in COVID screening area
• If HCW is performing an aerosol generating procedure like endotracheal intubation, adjustment of C-PAP or ventilator settings, nasogastric tube insertion, cardio-pulmonary resuscitation, etc.
• While respiratory sample collection of suspected COVID-19 patient
• While caring for known COVID-19 positive patient.

Table 2: Guidance for use of PPE in Different Healthcare Settings

| Setting                      | Target personnel | Activity                          | PPE type             |
|------------------------------|------------------|-----------------------------------|----------------------|
| COVID-ICU+WARD                | HCW+HSS          | AGP                               | Level-3              |
| Screening Area potential to have suspected COVID | HCW              | Screening                         | Level-2              |
| Non-COVID ICUs               | HCW              | Respiratory Sampling              | Level-3              |
| Emergency Sick Area          | HSS              | Disinfection/Patient Shifting     | Level-1              |
| Emergency Screening Area     | HSS              | Screening                         | Level-2              |
| Hospital Emergency Area      | HSS, HCW         | NAGP                             | TLM+HDG              |
| Screening general OPD        | HSS, HCW         | Screening                         | N95 mask, Gloves (Single) |
| General OPD                  | HCW, HSS         | Disinfection                      | TLM+HDG              |
| General Ward                 | HSS, HCW         | Disinfection/Patient Shifting     | TLM+HDG              |
| Laboratory personnel         | HCW, HSS         | Dealing Respiratory samples       | Level-1              |
| Radiodiagnosis               | HCW, HSS         | Drug Dispensing                   | TLM                  |
| If handling COVID Positive/suspect Ambulance (HCW travelling inpatient compartment) | HCW, HSS | Attending patient (Direct contact >15 min) | Level-2 |
| Dispensary                   | Pharmacist       | No Direct contact                 | Triple layer mask    |
| COVID Patient/Suspect        | Patient          | For Droplet prevention            | TLM                  |
| Offices Staff                | All staff        | Patient contact                   | TLM                  |
| Offices Staff                | All staff        | No Patient contact                | No PPE               |

HCW: Health care worker (doctor, nurses & technician), HSS: Hospital Support Staff (Cleaner/Sweeper/HA), NAGP: Non-aerosol generating procedure, AGP: Aerosol generating procedure, TLM: Triple layer mask, HDG: Heavy duty gloves

CDC website. Out of various procedures suggested, one should follow process for reuse as suggested by local health authorities.

General Cleaning[4]
1. Like other coronaviruses, COVID-19 can survive on various surfaces for 2 hours to 9 days, depending on a number of environmental factors
2. Clean frequently used objects/surfaces daily like phones, tablets, handles, keyboards, and switches, etc.
3. Common disinfectants such as 70% ethanol or sodium hypochlorite (0.5%) and diluted household bleach (1 part bleach to 9 parts water) used for one minute should be effective
4. List of household detergents effective against COVID-19 is available in https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2
5. Cleaning with soap and water can be done if surfaces are dirty
6. Clothes of COVID-19 suspected patients should be machine washed separately with warm water at 60-90°C and following any contact with such clothes, proper hand hygiene should be performed.
1. Though COVID-19 has not yet been detected in drinking water, like other coronaviruses, chlorination and disinfection with ultraviolet light as done in conventional, centralized water treatment methods should be effective.

2. If a centralized supply is not available, household water treatment methods, including boiling, using nanomembrane filters, chlorine, or UV irradiation, may be used.

Chemoprophylaxis[5]

The National task force for COVID-19 by Indian Council of Medical Research (ICMR) has recommended the use of hydroxy-chloroquine ONLY for prophylaxis in high-risk population viz. asymptomatic HCWs involved in the care of suspected/confirmed cases of COVID-19 and asymptomatic household contacts of laboratory confirmed cases. The doses recommended are 400 mg twice a day on day one followed by 400 mg once a week for seven weeks for health care workers and 400 mg twice a day on day 1, followed by 400 mg once a week for three weeks for asymptomatic household contacts of confirmed cases. However, in view of various side effects of the drug, it should only be given under prescription by registered medical practitioner. Further, as of now efficacy of the drug in above given setting has not been proven by randomized controlled trial.

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“Infodemic” of COVID 19: More Pandemic than the Virus

Abstract
Coronavirus disease (COVID 19), which was started in Wuhan, China in December 2019 has become a pandemic, leading to unprecedented risk to the human race. However, fear wave accelerating ahead of pandemic worldwide is driven by prejudice or erroneous information. This has been termed as “infodemics” by WHO considering its fake nature, which triggered discrimination and stigma of disease along with the failure of rapid response policies. Additionally, the lack of adequate pandemic preparedness plans identified in many countries may be responsible for infodemics. NonCOVID medical illnesses have taken a back seat at many places while implementing COVID 19 control strategies and patients are diverted to COVID 19 screening hospitals leading to a potential health crisis. Now, we also have to focus on mitigating infodemics and its implications at the social front while strategic planning to control current and future pandemics.

Keywords: COVID 19, fear, infodemics, pandemic

Introduction
Coronavirus disease (COVID 19), which was started in Wuhan, China in December 2019 has become a pandemic, leading to unprecedented risk to the human race. The majority of affected have mild illness resolving spontaneously, but 10%-15% of patients develop serious complications like acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure.[1,2] WHO and global leaders along with medical fraternity started tremendous efforts to protect citizens and contain this pandemic.[3] However, fear and panic wave accelerating ahead of the pandemic worldwide, which is being driven by prejudice or erroneous information. This has not only triggered discrimination and stigma of disease but also lead to hindrance in rapid response policies of health officials and policymakers.[4] While working in a pandemic environment, healthcare workers (HCW) have also developed physical and mental fatigue due to the loss of patients as well as their colleagues, creating fear and panics for them as well.[3] Such issues need to be addressed earliest and must be resolved.

“Infodemic” of COVID 19
As the COVID 19 cases continue to spread across the country, and the information about difficult to treat severe acute respiratory illness disseminate, information flows at much faster than the virus from social media and private unfiltered networks like WhatsApp, Facebook, Twitter, YouTube, TikTok, etc., Mostly such information about the illness is often derived from preliminary observations, and hence is often unreliable and speculative. However, it does lead to lots of confusion, panic attacks, and anxiety amongst citizens. This situation was recently described as “infodemic” by the World Health Organization (WHO).[6] Commenting on the burning issue of COVID 19 globally, social media like Wall Street Journal also used “infodemic” quoting as “when unreliable information spreads far and wide”. [7] Such uncontrolled information can be dangerous in the sense that policies implemented to control the pandemic become more difficult. Hence the important factor in the current pandemic is to provide authentic information from reliable sources.

Infectious Disease and Psychology
We know people response to highly infectious diseases can lead to the development of fear, stress, anxiety, sense of insecurity, and prejudicial behaviors, especially when the infectious disease outbreak is sudden with rapid spread, making it pandemic along with fatalities.[4] In history, epidemics of infectious disease...
have been associated with specific community groups, which prompted fear, stigma, and discrimination to concerned ethnicity. This has been observed in outbreaks of typhus fever and cholera in Russian Jewish immigrants, bubonic plague in Chinatown community, hantavirus infection in Native Americans, severe acute respiratory syndrome (SARS) outbreak in the Chinese population.\[8\] Previous studies had documented similar reactions with inability to implement containment measures for infectious diseases like tuberculosis, leprosy, and HIV/AIDS. The fear and anxiety of being labeled as a potential source to transfer SARS were so traumatizing for patient’s subgroup that it created stigma for whole society.\[9\]

Fear and stigma of the disease usually go hand in hand and fearful minds can lead to hatred or stigmatize a subgroup of the population. This stigma can be related to a particular race, region, descent, and country where the disease started but can go up to continents and beyond.\[8\] In an attempt to contain the pandemic, WHO and other national authorities have advised isolation of active cases, quarantine of close contacts, sealing off hotspots, nationwide lockdowns, and domestic travel and visa cancellation with an aim of stopping international travel. While it helps in controlling the spread of disease, this also causes fear, discrimination, and suspicious behavior amongst the people and may affect important supply chains. It also can lead to the development of not only obsession and multiple somatic complaints like chest tightness, difficulty in breathing but also the occurrence of insomnia, lethargy, loss of concentration, anger, and depression.\[8,10\]

**Impact of Fear of Disease**

Epidemiological studies about infectious disease outburst showed that though the general population needs prompt information related to the latest development, a high-risk subgroup is exposed to the danger of fear, stigma, and discrimination of disease, which needs to be addressed by healthcare professionals and policymakers. This stigma with fear of disease in AIDS had adversely impacted the testing and treatment of infected patients. Similar unwillingness for testing and treatment of tuberculosis has been noticed by medical staff in an immigrant population. Also, studies have shown that the incidence of posttraumatic stress disorder (PTSD) increases after any infectious outbreak.\[8,6\] The classical example of such an illness is SARS, which gave rise to global anxiety due to highly contagious nature and rapid spread through international travelers. Some amount of panic reaction can be rational, but high mortality rates and epidemic spread of such outbreaks can have a more harmful impact in the form of anger, blaming, and violence against people from the area of disease origin.\[8\]

Due to social media infodemics, people got more confused and became hyperreactive leading to unbelievable scenarios in the current COVID 19 pandemic.\[10\] As the disease can spread from droplets, people have manhandled persons in the public places after sneezing due to the fear of disease. When isolation of cases or contacts started and lockdowns imposed as a control measure, some people not only noticed weariness and loneliness but also feared that lead to occasional suicidal tendency. One person jumped off from terrace to end his life due to the fear of disease when he was hospitalized for COVID 19 while another has killed himself to protect his community members. People from disease hotspots are so scared that they are not going out for the treatment of other ailments as well. Villagers’ reaction is so furious that they are not allowing people from urban areas to enter into their villages, with an idea that this infection is of an urban area and should not come into the rural area. Also, as there is no specific treatment or vaccine for COVID 19 till now, it is fueling more fear among the general population.\[10,11\]

HCW also develop psychological effects due to COVID 19 when it leads to intense workload along with the fear of getting infected while handling patients on a large scale.\[8\] Print and social media reports incidents of HCW facing discrimination and not allowed to come back to their home and also rejected by asking them to evacuate rented premises.\[11\] Unavailability of sufficient personal protective equipments have already created a fearful wave in minds of HCW, which impacted in a hazardous way to close down their daycare clinics or OPDs. Like everybody, HCW are also exposed to rumors and wrong information from social media infodemic apart from exposure to infected patients, fueling in their apprehension to work in an infected environment. This is further strongly affected by increasing stigmatization and mistrust among their societies.\[6,12\] Discrimination and racism going on peak especially for Asian people after social media posts accusing a country about using the virus as a bioweapon, which created many theories and conspiracies. This pandemic is exposing all negative aspects of human mentality rather than solidarity.\[11,13\]

**Strategies to Counter Fear of COVID 19**

To mitigate the fear of infectious disease outbreak and counter all the infodemics related to it along with protecting public health is complex but an important part of public health crisis management. All harmful impacts of fear of disease need to be evaluated and managed with the help of mental health experts with behavioral modification and spreading awareness, which helps in preventing stigmatization of the population at risk.\[8\]

The most integral step to reduce this fear and stigma of COVID 19 is education and authentic transparent information from reliable sources. This rapid dissemination of authentic information is of the greatest importance not only for the prevention and control of epidemic outbreak but also the infodemic. Motivating people about preventive measures like hand washing, use of masks, and social
distancing while in a public place through educational campaigns is important. A 24 × 7 helpline along with daily press release policy like situation updates as is being done by many national authorities is a significant step towards containing misinformation.[11] Celebrities and national leaders should open up on social media when affected by COVID 19, which can remove the stigma and improve willingness for self-screening of disease. This transparency of epidemic information can inspire the general public to report their symptoms of disease and travel history. Social media like television, radio channels, newspapers, and private networks connected through the internet should be utilized for promoting the myth buster educational materials. Additionally, public and private hospitals should activate mental health clinics, which can address panic reactions along with removing rumors or doubts among the general population.[11,14]

Another important tool is developing the behavioral strategy to answer the needs of ethnic groups facing the stigma and discrimination of disease. This is an excellent complementary strategy for general health educational campaigns, which can be appropriate to the personal needs of affected ones by forming a community outreach team for the behavioral strategy implementation. The team can document and monitor the reactions and ideas of people leading to stigmatization. This team makes a special focused plan with community field visits, group discussions, rapid situational assessment, and response with targeted health educational materials. This can create awareness with better evidence-based information; removing myths, misconceptions, and reserved thoughts; motivates to create community resilience among peoples at risk; and providing reassurance with integrity to affected ethnic groups at an individual level. Such a strategy had been successfully utilized during the SARS epidemic.[9]

Employers should stress up about the importance of personal preventive measures and clarify organizational policies for responding about COVID 19 cases among staff members while maintaining privacy and confidentiality. This can remove fear, stigmatization, and discrimination of being affected and ensure a secure job after complete recovery.[15] Stamping on the hand of a person infected with COVID 19 and house labeling having an infected person may not be a good idea in the current pandemic; rather it may increase the discrimination among society and people having symptoms suggestive of COVID 19 and people may not come forward for testing.

Finally, we have to keep in mind and gear up for upcoming PTSD in the current fearful scenario of this COVID 19 pandemic with a multidisciplinary approach. This may include the formation of mental health teams, which includes psychiatrists, clinical psychologists, and trained nurses; developing electronic apps for psychological counseling; addressing the personal needs of the large populations for wider reach; and rapid communication of updated COVID 19 situation regularly.[16,17]

**How to Fight an Infodemic**

It is reasonably apparent now that fear of virus (F-virus) created by social media is more contagious to the general population than COVID 19 itself. To fight this infodemic of COVID 19, WHO has a newly launched information platform called WHO Information Network for Epidemics (EPI-WIN), which provides advice and guidelines to various professionals and also receiving information.[6] Especially, paying attention to trustworthy information, taking a break from social media coverage, exercising, and dedicating time with family and friends are recommended for coping with stress while staying at home in lockdown.[15] While fighting this infodemic causing panic everywhere, we have to flourish new mental contagion, which is of healthy ideas, boldness, and solidarity. This is not a time to divide over ethnicity, nationality, or regionalism as the virus does not respect international borders. This is a time for global cooperation to fight back against the virus.[6]

**F-virus and Non-COVID Health Side Effects**

Patients suffering from nonCOVID chronic diseases being unable to access the required medical care have come to light and some have even lost their lives. The closure of services like regular OPDs and surgical or other facilities requires a relook. This F-virus may have contributed to the worsening of co-morbid conditions like diabetes, hypertension in elderly patients with or without COVID-19 and may be contributing to higher mortality in them. Media reports from India that patients with kidney failure denied lifesaving dialysis and the patient’s cancer chemotherapy is delayed in the absence of laboratory reports.[11] COVID 19 screening being asked in many tertiary care hospitals before any treatment or elective surgery, which has now become a standard prerequisite.[19] This collateral damage caused by COVID 19 is immeasurable and mostly being overlooked for the time being but maybe causing more morbidity and mortality than COVID 19 itself. Additionally, the lack of adequate pandemic preparedness plans, which may be due to economic and human resource limitations, leads to higher mortality rates[19] and maybe a factor responsible for infodemics. Social injustice and discrimination leading to communal violence has been already known in previous pandemics[20] and can occur during COVID 19 pandemic crisis for which we need more vigilance and be prepared to tackle debacle.

To conclude with a positive note, this pandemic of COVID 19 is still not settled in many countries, but will not last forever if we follow social distancing, hand hygiene, and cough etiquettes without the fear and stigma of the disease. For which we need to invest more in strategic planning to counter this worldwide infodemic.
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