Guidelines and position statements for COVID-19

Indian Society of Nephrology - Covid-19 Working Group

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Chapters

Chapter-1:

An overview of epidemiology, genomic structure, the molecular mechanism of injury of lung and kidney in coronavirus infection

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Abstracts:

COVID-19 is a novel beta coronavirus strain that was first discovered in 2019 in Wuhan city of China. Based on virus genome sequencing studies, the bat is suspected as the natural host of virus origin, and COVID 19 might be transmitted from bats via unknown intermediate hosts like reptiles and snakes, etc. to infect humans. COVID 19 is primarily transmitted from person to person contact via droplet infection within the incubation period or after clinical manifestations of fever, cough, sneezing, sputum, dyspnea, and pneumonia. Covid 19 enters the respiratory tract through the ACE2 receptor on alveoli through binding of s-protein of the virus and may cause injuries though the cytopathic effect, as well as cytokines and other mediators, release 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 a rise in serum creatinine and blood urea nitrogen. Kidney involvement is an independent risk factor for mortality. The purpose of the article is to introduce coronaviruses, its genomic structure, mechanism of injury of lung and kidney.

Keywords: Coronavirus; severe acute respiratory syndrome; pneumonia; sepsis; mechanisms; acute kidney injury

Introduction :

Coronaviruses (CoV), are amongst the newly emerging virus, which affects zoonoses and transmitted between animals and human beings (1). In the past, It 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)(2). The SARS was transmitted from civet cats to humans and MERS from dromedary camels to humans. Many other coronaviruses are still circulating in zoonoses that are not found in humans to date.(3,4,5)

COVID-19 is a novel CoV strain that was first discovered in 2019, which was not previously reported in humans(6). This CoV was renamed several times after discovery, first of all, as a newly identified β-coronavirus in Wuhan in late months of 2019.On 12th January 2020, the World Health Organization (WHO) renamed it as the 2019-novel coronavirus (2019-nCoV), and on 11th February 2020 again officially rendered it as coronavirus disease 2019 (COVID-19). On the same day, the Coronavirus Study Group of the International Committee on Taxonomy of viruses of WHO proposed the name SARS-CoV-2 for this virus.(7,8,9). At the end of 2019, COVID-19 caused a cluster of pneumonia cases in Wuhan, a Chinese city, on 30th January, the outbreak was declared as Public Health Emergency of International Concern (PHEIC) and now a declared global pandemic by WHO(10). As of date 21st March 2020 WHO reports, there are 266073 confirmed cases, and 11,184 confirmed deaths in 183 countries. The epicenter of pandemic changed from Wuhan city in China to Italy and Spain in Europe.(11,12)

Structure and viral genome of coronavirus in brief:

The Covid-19 or SARS-CoV-2 is a β-coronavirus, which is enveloped non-segmented positive-sense RNA virus of subfamily *Orthocoronavirinae* of the *Coronaviridae* family (10,13)]. 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.(13,14) In the past, six CoVs were discovered as a human-susceptible virus, 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 [2,13]. COVID19 one strain of SARS-CoV-2 is 29.9 kb (14), While SARS-CoV and MERS-CoV have positive-sense RNA genomes of 27.9 kb and 30.1 kb, respectively (15). It has been shown that the genome of CoVs contains a variable number (6–11) of open reading frames (ORFs) (16).

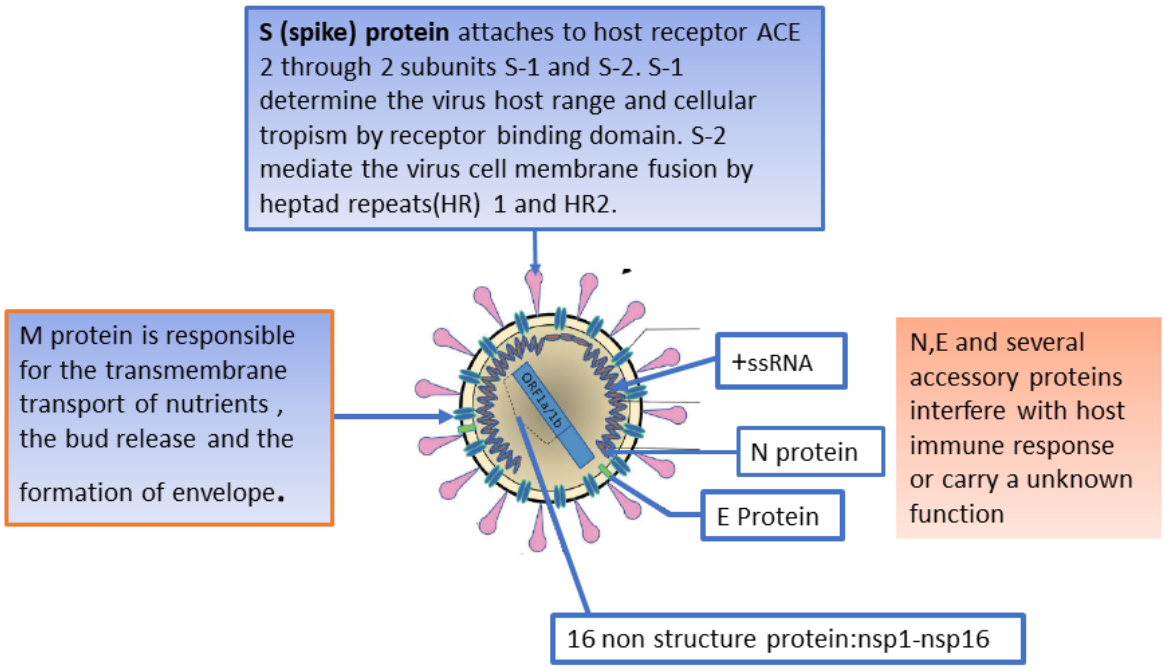

Figure-1 depicting the structure of the Coronavirus and the role of different proteins.

Figure-1 depicts the structure of the CoVs. CoVs are round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. The single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 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 (17,18).

The sequencing studies of Wu et al.(19)) revealed genomic and phylogenetic similarity of COVID 19 with SARS-CoV, particularly in the S-protein gene and 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-CoVZXC21 and 82% with that of human SARS-CoV (4). For this reason, the new virus was called SARS-CoV-2 (20). The majority of genomically encoded proteins of COVID-19 and SARS-CoVs were similar, except few differences in some amino acid substitutions in NSP2, NSP3, spike protein, receptor binding domains (20,21). Another recent research suggested (22) 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. (23) revealed that COVID 19 was mutating in different patients in China. Tang et al. (24) 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 reptiles and snakes, etc. to infect humans.

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 (25). ACE2 is cell receptor for COVID 19 and regulates the transmission across the species and between human beings as well (26,27). S-protein contain two subunits, S1 and S2 (28,32). S1 determines the virus-host interaction and cellular tropism with the vital function domain- receptor-binding domain(RBD), while S2 mediates virus-cell membrane fusion by two tandem domains, heptad repeats 1 (HR1) [27] and HR2 (30).

S-protein and ACE2 binding efficiency of COVID-19 is 10- to 20- fold higher than that of SARS-CoV (31). For SARS-CoV, the cleavage of trimer S protein is triggered by the cell surface-associated transmembrane protease serine 2 (TMPRSS2) (32) and cathepsin(33), 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 (34), which encode non-structural proteins, and form replication-transcription complex (RTC) in double-

membrane vesicle (35). Continuously RTC replicates and synthesizes a nested set of subgenomic RNAs (36), which encode accessory proteins and structural proteins. Mediating endoplasmic reticulum (ER) and Golgi [37], 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, maybe area of interest and research in future (13).

Mechanisms of kidney injuries:

Host susceptibility, particularly elderly and peoples with underlying diseases, hypertension, cardiac diseases, bronchial asthma, diabetes etc. influence the progression of COVID 19 infection. The mechanism of kidney injury by COVID-19 appears multifactorial and, although precisely, remains unknown.(38) 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 (39,40). The molecular study showed CoV 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.It is a fact that ACE2 expression is 100-fold higher in kidney tissues than the lung(41). 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(42).

The other piece of information could be inducing sepsis and the cytokine storm theory(43). The cytokines and other mediators are released after CoV infection leading to sustained inflammatory response lead 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 (44). It contributes to AKI indirectly through the effects on renal tissues, because of hypotension, hypoxia, shock, and rhabdomyolysis. However, such patients develop kidney injuries otherwise also.

Epidemiology of COVID-19:

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 (45). 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 (46,47). The droplets do not travel more than 6 feet and do not linger in the air also. However, a report revealed that SARS-CoV-2 might remain viable in aerosols under experimental conditions for at least three hours (46). 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 (48). 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 to 5% among tens of thousands of close contacts of confirmed patients in China (49). In the United States, the symptomatic secondary attack rate was 0.45% among 445 close contacts of 10 established patients (50). 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(49).

Sample collection and diagnosis: 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 (naso- and oropharyngeal samples); and lower respiratory tract such as sputum, endotracheal aspirate, or bronchoalveolar

lavage(BAL). The collection of BAL samples should only be performed in mechanically ventilated patients. The samples require storage at four degrees celsius.

In the laboratory, a reverse 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. The probes used are based on the initial gene sequence released by the Shanghai Public Health Clinical Center & 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.

Clinical features:

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 frequent manifestation of severe infection, characterized primarily by fever, cough, dyspnea, and bilateral lung infiltrates on chest imaging (51,52,53). In a study describing 138 patients with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of illness were fever in 99%, fatigue in 70%, dry cough in 59%, anorexia in 40%, myalgias in 35%, dyspnea in 31% and sputum production in 27% (52). Besides lung, kidney involvement also seems to be frequent in symptomatic patients with positive tests. They manifest clinically with proteinuria, hematuria, rise in serum creatinine, and blood urea nitrogen with AKI, an independent risk factor for mortality.

India specific situation: As of March 23, 2020 (54), 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 seven 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 the 10 crores will face severe COVID infection (55). Looking at the incidence of 5.1% of AKI in severe cases (38), there would be 5.1 million AKI patients because of Corona, and presumably, half of them may require renal replacement therapy. It is estimated that with community spread 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. However, India can handle the case if the infection spread slowly over a year.

AKI and SARS-CoV-2:clinical manifestations and case fatality

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

Although SARS-CoV2 or COVID-19 causes 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 also need to be explored (15,16). It has been reported that SARS-CoV and MERS-Co-V have infected more than 10,000 people in the past two decades, with mortality rates of 10% and 37%, respectively (56,57). In 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 (58). 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 (42). Kidney involvement was a strong and independent predictor of mortality as during the

SARS and MERS outbreak, that hints out for the special attention for the kidney involvement with COVID-19 infection as well.

The incidence of AKI with COVID infection reported varying from 3%- 9%. (53,59,60,61). A larger prospective study has reported the overall incidence of 5.1% (38). In a study of 59 COVID-19 infected patients with 28 severe cases and three deaths, Li et al. (62) found that 34% of patients had albuminuria on the first day of admission, and 63% developed proteinuria during the hospital stay. Nineteen percent of people showed an elevated level of plasma creatinine. Blood urea nitrogen was elevated in 27% of patients and in two-thirds of patients who died. 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.

In another more extensive prospective study, Cheng Y et al. (38) studied 701 patients (median age 63 years with interquartile range, 50-71 years, and 367 male) admitted in a tertiary teaching hospital with 3 branches in the province following this 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 haematuria. The prevalence of elevated serum creatinine elevated blood urea nitrogen, and estimated glomerular filtration 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 blood urea nitrogen (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 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 ration of mortality also increased with the degree of proteinuria and haematuria. 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% was significantly higher than patients with normal baseline serum creatinine (13.2%). However, the major limitation of the study was that many patients might have concurrent chronic kidney disease.

The JAMA study with 27314 case records showed the overall case-fatality rate was 2.3% in confirmed cases, about 15% elderly patients, in particular those aged ≥ 80 years, 8% in 70 to 79 years of age. About 50% patients who died had comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases. The disease was uncommon in very young, and fatality was also very low. (63) The previous study on SARS-CoV, which revealed the fact that the acute kidney injury (AKI) was uncommon in SARS-CoV but accounted for the fiercely high mortality of 91.7%, notably 33 out of 36 cases, died (42). The incidence of in-hospital death in patients with elevated baseline serum creatinine was 33.7%, which was significantly higher than in those with normal baseline serum creatinine (13.2%) (38).

Treatment strategies for in general for COVID and with AKI :

At present, the management strategies of COVID-19 with AKI is conservative with good hydration, nutritional support, and paracetamol with aiming for the self-recovery of the patients in the quarantine. The patient with respiratory distress may require oxygen therapy and intensive care with ventilatory support in case of acute respiratory distress syndrome (ARDS). 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 Caregiver should also use appropriate approved protective masks and clothes.

There is no effective antiviral therapy available. In the most extensive 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 antivirals were used, including arbidol hydrochloride, ganciclovir, interferon, lopinavir and ritonavir, oseltamivir, and ribavirin. However, there was no significant difference between patients with AKI and those without AKI (38).

The most recent NEJM study of the randomized controlled trial (64) showed no mortality benefit of treatment with lopinavir-ritonavir (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 (65), which may divulge results in April of this year. Chloroquine phosphate showed some efficacy against COVID-19–associated pneumonia in a multicentre clinical trial conducted in China(66). The National Taskforce for COVID-19 by ICMR recommended the use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection for selected individuals like asymptomatic 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 asymptomatic 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; that 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, other preventive measures and quarantine process should remain continued. (67,68)

Few retrospective analyses showed benefit with the use of glucocorticoids in SARS-CoVinfection(69,70). Metanalysis on the use of glucocorticoids in previous SARS-CoV infection do not support the use of glucocorticoids in COVID infection 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(71). WHO does not recommend the use of steroid expecting potential inhibition of viral clearance and prolongation of the duration of viremia(72).

Experimental therapies:

There are several future promising therapies are being evaluated and in pipeline. The use of convalescent plasma(clinical trial ChiCTR2000029757), monoclonal antibodies like Tocilizumab, a monoclonal antibody against the IL-6 receptor are under underway (ChiCTR2000029765) awaiting reports, a monoclonal antibody directed against the Ras-binding domain of the S- protein of MERS-CoV are under investigation. However, no such evidence is available against COVID-19 are under underway and awaiting reports.(58)

Extracorporeal therapy:

The indirection 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 promising. CRRT was successfully used in the treatment of SARS, MERS, and sepsis in the past (73,74). 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 (75).

In summary, COVID 19 is a novel Beta CoV infection which has genomic homology with Bat CoV and transmitted to human beings through some 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, the kidney involvement 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 management strategies applied for AKI in COVID are supportive care with awaiting self-recovery.Many patients with AKI may progress to CKD in future. COVID infected patients need to be quarantined.

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Chapter-2:

COVID 19 in patients of Chronic Kidney Disease and Hypertension

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The prevalence of chronic kidney disease (CKD) is very high in all parts of the world, including India. Many CKD patients will also acquire SARS-CoV-2 infection. CKD patients receive multiple pills for hypertension, metabolic bone disorders, and anemia management. The most important of them are anti-hypertensives, which include calcium channel blockers, centrally acting drugs like clonidine, Beta-blockers, Alpha-blockers, and Angiotensin-converting enzyme inhibitor, and angiotensin receptor blockers.

Many patients of CKD will experience episodes of acute kidney injury after COVID-19 infection, and the renal function will deteriorate after infection leading to acute on chronic kidney disease. Such a decline in kidney function depends on the severity of the infection. SARS-Cov-2 may affect the kidney directly through ACE2 receptors causing direct injury, glomerular injury by affecting effector T cell or immune-complex formation, and as a part of cytokine storm theory after virus-induced sepsis.

Is there an increased risk of COVID 19 in patients on renin-angiotensin blockers?

As is evident from literature, 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, these patients may be at higher risk of infection due to the availability of increased receptors (1, 2). Also, with evidence of higher mortality in patients of hypertension, diabetes, cardiovascular disease and old age (3), there was a hypothesis raised, whether the use of ACEI / ARB, which is common in these subsets of patients, can increase the risk and potential threat to COVID 19 infection. This had a major impact on the management of hypertension, and people were concerned regarding the use of RAAS blockers. However, there was immediate rebuttal from various societies, including the European Society of Cardiology, stating that there was no such evidence of ACE-2 activity and COVID 19 associated mortality (4).

Relationship of RAAS blockers and COVID 19 infection:

It was pointed out that there are no data on how many of those who died with COVID 19 were on ACEI/ARBs. It was also emphasized that being on these drugs is possible because of more comorbidities like diabetes, hypertension, kidney disease, 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 (5). It was also explained that high Angiotensin II (in severe cases or in the absence of ACEI/ARB) can open 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 cardiovascular patients, rather than its inhibition, renders them more prone to a deleterious outcome (6).

Anti-hypertensives other than ACEI and Angiotensin 2 receptor blocker:

Guideline: We suggest continuing ACEI and ARBs for anti-hypertensive and renoprotective purposes. We suggest continuing other anti-hypertensives as before unless there is some specific contraindication that appears during the infection like hypotension.

Is there any need for changing medications for 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 well studied. At present, there is no evidence to suggest stopping EPO. Oral iron therapy should be continued, and the use of Intravenous Iron should be discouraged.

Guidelines: We suggest continuing anemia therapy as before the COVID.

Should patients continue medications for CKD-MBD:

Medications for CKD-MBD should be continues as before unless there are specific contraindications that appear during the management of COVID 19 infection.

Conclusion

The speculation about the ACEI / ARB use and COVID-19, at present, has no scientific basis or evidence to support its withdrawal. The council on hypertension of the European Society of Cardiology recommended that physicians should not withhold

these drugs as they are beneficial and might be rather protective against serious lung complications in COVID 19 infections. This was soon followed by several other societies like the International society of Nephrology, suggesting inadequate evidence to stop RAAS blockers in patients.

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Chapter-3

Guidelines for hemodialysis for COVID19 patients

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COVID-19, a disease caused by a novel corona virus, is currently a pandemic, which particularly affects and produces high morbidity in the elderly and in patients with comorbid conditions. Uraemic patients on maintenance hemodialysis are particularly vulnerable because of; their existing comorbidities, repeated unavoidable exposure to hospital environment and possible immunosuppressed state due to CKD status and immunosuppression they may be receiving. These patients are therefore more prone to develop severe infectious diseases compared to general population. The close contact of patients and unit staff may also increase the risk of two way transmission. Therefore, all units need to put into practice systems to continue providing dialysis, while ensuring the prevention, mitigation and containment in haemodialysis centers of the emerging COVID-19 pandemic. Even a single patient or staff member, without symptoms can potentially infect a large number of other patients and coworkers. A special situation will also arise as some patients in isolated areas who develop acute kidney injury (AKI) will require to be provided renal replacement therapy. These guidelines are therefore suggested for all hemodialysis units of India by the Indian Society of Nephrology. Please note that the pandemic of CORONA 19 is rapidly evolving so also is the data and research about this disease evolving almost every day. Hence; though most of these guidelines are valid, a reader is advised to keep up to date from advisories given by health authorities.

We recommend that all 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.

We recommend that all units should make an effort to educate their personnel in hemodialysis units; including Nephrologists, Nurses & technicians & other staff and all patients undergoing maintenance hemodialysis along with their care givers at home & accompanying persons, about COVID 19. This information should be given by arranging special classes and group meetings. Also the information should be prominently displayed in the HD unit and waiting areas. The information including images for education can be obtained on the International Society of Nephrology website https://www.theisn.org/covid-19

We suggest that all patients should be instructed not to decrease or miss their hemodialysis sessions.

We emphasize that uremic patients are especially vulnerable to this infection and may exhibit greater variations in clinical symptoms and infectivity. Patients with COVID-19 infection on maintenance hemodialysis still need to come to the dialysis center for regular dialysis. In this situation it is important for dialysis doctors and nurses to reemphasize the importance of not missing dialysis by all means of communications. Complications resulting out of missing dialysis session may lead to admission, which may in fact expose the patient to longer hospital stays and higher risk of this infection.

We recommend that all units instruct their patients to recognize early symptoms of this infection and call their treating doctor or dialysis technician before coming to dialysis center. The unit should make necessary arrangement for their arrival or triage them.

We suggest that patients having the following symptoms do not directly enter the dialysis unit but remain in a specially designated area and contact the unit staff for further instructions. This area should be clearly marked and all patients at entry to HD unit should be asked about these symptoms before giving them access to the unit: Recent Onset fever, Sore throat, Cough, recent Shortness of breath/dyspnea(without major interdialytic weight gain), Rhinorrhoea, Myalgia/bodyache or fatigue and Diarrhea.

We recommend that, patients should be advised to report to their treating nephrologist about; history of contact with a diagnosed case of COVID 19 or coming in contact with person who has had recent travel to foreign country or from high prevalence area within our country as notified by the Central and state governments respectively.

We recommend that patients should inform staff of fever or respiratory symptoms immediately upon arrival at the registration desk.

We recommend that dialysis doctors and nurses make an attempt to actively obtain such history from all patients, using leading questions where necessary.

We recommend that patients with symptoms of a respiratory infection should put on a facemask at check-in and keep it on until they leave the unit. The unit staff should make sure an adequate stock of masks is available to provide to the patients and one accompanying person if necessary. Patients who are stable on HD may be recommended to come to the unit alone.

We suggest that dialysis units designate special waiting areas for patients who are possible or proven cases of COVID 19, where possible. These areas should have a sitting area permitting a distance of at least 2 meters between 2 patients. Where this is not possible, patients may wait in their own private vehicles until they receive specific instructions from the unit staff. There should be an area for initial symptoms check and temperature measurement of all patients before they are sent to area for possible or proven COVID 19.

We recommend that HD units which cannot provide such area should liaison with units that can provide such area to take over their patients of possible or proven COVID 19.

We recommend that instructions to patients and relatives should be prominently displayed in the waiting area of the dialysis unit as well in any other lobby or public space in the hospital in the local language as well as Hindi and English.

We suggest that any possible case among dialysis patients be examined by the dialysis doctors/ treating nephrologist prior to entering the unit.

We recommend that all patients with suspected but unproven infection be tested as per the local health authorities' guidelines using appropriate sample as per ICMR guidelines.

Rationale: All dialysis patients mandatorily visit a dialysis unit or hospital twice or thrice a week for a life saving treatment. It is hence not possible for dialysis patients to practice total home quarantining or social distancing as is recommended for most individuals. Furthermore many of these patients carry additional risk factors like diabetes, hypertension, CKD itself and ACE inhibitor therapy and are likely to develop more severe disease. The logistics of isolating all unproven but highly suspicious cases

may place a severe strain on the resources of some dialysis units hence these patients should probably be tested and managed in accordance with local guidelines

We suggest that specific instructions be given to patients having symptoms while dialyzing in a unit which include:

- Covering mouth and nose with a disposable tissue (The unit may provide these) when coughing or sneezing or using the inside of the elbow. This may be displayed in pictures which are available from the CDC website https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/dialysis.html
- 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.
- Immediately wash hands with soap and water for at least 20 seconds. If soap and water are not readily available, clean your hands with a hand sanitizer that contains at least 60% alcohol.
- Wear a facemask when around other people (e.g., sharing a room or vehicle) and before entering a healthcare provider's office.
- If unable to wear a facemask (for example, because it causes trouble breathing), then cover coughs and sneezes, as above and dialysis personnel, attendants and caregivers should wear a facemask if they enter your room.
- All patients who are coughing or sneezing should be encouraged to wear a face mask.

We suggest that instructions (in appropriate languages) about hand hygiene, respiratory hygiene, and cough etiquette, instructions should include how to use

facemasks, how to use and dispose of tissues and contaminated items in waste receptacles, to cover nose and mouth when coughing or sneezing, and how and when to perform hand hygiene be prominently displayed. Standard images can be obtained from the same website mentioned above.

We suggest that all patients with either a positive test for COVID 19 or recent exposure to a positive case or with highly suggestive symptoms awaiting testing be dialysed in isolation.

The isolation may take the form of a separate room with a closed door, which is ideal 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. Even in this situation it is necessary to physically separate areas for proven positive and suspected cases. Where this is not possible we suggest that the positive or suspected patient may be dialysed at a row end within the unit ensuring a separation from all other patients by at least 2 meters. This is in addition to all the precautions to be followed by the patients and the staff of the unit caring for such patients.

Rationale: With the recognition of asymptomatic carriers who may shed the virus from 2 to 14 days and may not undergo testing as well the figures showing only mild symptoms in 85% of patients, it is necessary to ensure that a single patients in a unit does not become the source of an outbreak.

We suggest that dedicated areas have disposable tissues and waste disposal bins placed next to each dialysis chair / bed and nursing stations to ensure adherence to hand and respiratory hygiene, and cough etiquette.

We recommend that each dialysis chair / bed be equipped with an appropriate alcohol-based hand sanitizer within reach of patients and staff.

We suggest that units ensure dedicated staff caring for suspected or proved cases where possible who do not look after other patients during the same shift.

We recommend that dialysis staff be given special instruction in infection prevention and precautions by infection control nurses where available or by doctors in the unit using the CDC material available on its website supplemented by video aids available at the link provided.

We recommend the use of all personal protective equipment for dialysis doctors and nurses looking after proven or strongly suspected patients of COVID 19:

This will include shoe covers, gown, alcohol hand rubs, surgical cap or hood, goggles or eye shields, for those not using spectacles, mask and surgical gloves. Ideally all masks should be N95 respirators with filters, however as the life of such masks is approximately 8 hours and they can be uncomfortable over a long term and are in short supply they should be prioritized for aerosol generating procedures, namely intubation, open suction and bronchoscopy. Surgical trilayered masks and cloth masks can be used as alternatives for all other procedures.

The correct method of donning and doffing PPE can be viewed on youtube at https://www.youtube.com/watch?v=kKz_vNGsNhc

We suggest avoiding of eating in the unit by staff where possible and where necessary that staff separate their meal times to avoid congregating in the same area. Talking during meals should be minimized to reduce the spread of droplets

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.

We recommend that used 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 minutes before sluicing and then be transported for laundering after each use.

We recommend that all dialysis unit staff follow the following practices

Wash your hands often with soap and water for at least 20 seconds especially after you have been in a public place, or after blowing your nose, coughing, or sneezing. It should be done before approaching any patient.

If soap and water are not readily available, use a hand sanitizer that contains at least 60% alcohol. (AHD2000 or AHD 3000). Cover all surfaces of your hands and rub them together until they feel dry. The seven steps of hand washing should be strictly adhered to and the same steps used for use of an alcohol based hand sanitizer.

Avoid touchingyour eyes, nose, and mouth with unwashed hands.

These measures will protect you, your fellow staff members and the patients you are looking after. If hands are visibly soiled or dirty they should be first washed with soap and water and then an alcoholic hand rub used.

We recommend that all units 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 bed linen be changed between shifts and be soaked in a 1% hypochlorite solution for 20 minutes before sluicing and transported for laundering.

Ifsurfaces are dirty, clean them**:** Use detergent or soap and water prior to disinfection.

We recommend that solutions composed either of hypochlorite or alcohol, formaldehyde or glutaraldehyde based be used for disinfection of surfaces in accordance with the manufacturers 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?

To make an appropriate bleach solution, mix:

1 liter of Medichlor with 9 liters of water. This solution is usable for upto 24 hours after which it has to be discarded and a fresh solution prepared.

As an alternative 10 Grams of household bleaching powder can be dissolved in a liter of water and used for a period of 24 hours.

Alcohol based solutions.

Ensure solution has at least 70% alcohol.

Appropriate commercially available solutions include Aerodosin a mixture of isopropanol, glutaraldehyde and ethanol or lysoformin a mixture of formaldehyde and glutaraldehyde

Almost all common disinfectant solutions are effective in killing the virus on surfaces, the key is effective and frequent cleaning.

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.

We suggest separating equipment like stethoscopes, thermometers, Oxygen saturation probes and blood pressure cuffs between patients with appropriate cleaning and disinfection in between shifts.

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.

We recommend that any patient with suspected or proven infection be admitted in accordance with the local and National Health authorities' guidelines.

We recommend that notification of positive cases be done in accordance with local and national guidelines for the same.

We recommend that dedicated dialysis facilities be made available for patients with severe COVID 19 disease admitted in special isolation areas that develop AKI.

We suggest that all modalities of renal replacement therapy (intermittent hemodialysis, peritoneal dialysis, prolonged intermittent renal replacement therapy or continuous renal replacement therapy) may be used for patients with AKI depending on their clinical status.

A small proportion of patients between 3 to 15% of COVID develop AKI, largely due to cytokine storm. The disease is usually mild but a small number can be anticipated to

require renal replacement therapy (RRT). An 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. As isolation wards either existing or carved out of normal working space are set up to isolate and treat COVID cases, most will not be equipped with plumbing, treated water or drains to use for hemodialysis. The use of spouts on existing drain lines ensuring an air fluid gap and portable SS tanks or water treatment systems to provide water for hemodialysis machines can allow intermittent HD and SLEDD. (See Indian Society of Nephrology guideline on setup of a dialysis unit for details).

CRRT machines are free standing and can function anywhere in the hospital using sterile bagged replacement fluid and dialysate, but operating costs are high. In this regard, the use of acute peritoneal dialysis can be life saving and should be considered as a bridge therapy as was demonstrated in observational studies like the 0 by 25 study. Once a patient has been treated and completed the 14 day isolation period or is stable for shifting, he can be treated in other areas of the hospital as mentioned above.

We suggest that the use of cytokine removal therapies with Cytosorb, Oxiris and other similar devices is unproven and is not recommended except, where other indications for RRT exist or in the context of a clinical trial.

The role of IL-6 in the pathogenesis of ARDS of COVID 19 has received much attention, with studies indicating that a cytokine storm associated with elevated levels of IL-6, IL-18 and IFN gamma are associated with more severe disease and higher mortality. Monoclonal antibodies targeting individual cytokines have been tried in small case series, which reported a benefit. Extracorporeal therapies using high volume hemofiltration or adsorption to decrease cytokine levels may theoretically be expected to confer benefit and 1 study of HVHF at 6L/hr showed cytokine reduction and

improvement in SOFA scores in septic patients. Paradoxically studies with the Cytosorb device showed either unchanged or even increased Il-6 levels in small studies and no study on extracorporeal therapies in sepsis has provided evidence of mortality benefit so far. The Oxiris hemofilter is heparin bonded and is used for CRRT in patients requiring RRT for conventional indications and is also claimed to reduce cytokine levels. At present this area needs more research before any definite recommendations can be made.

Chapter-4:

Transplant specific guidelines during covid-19 outbreak

Vivek Kute, Santosh Varugese, Narayan Prasad, and Sanjay Kumar Agarwal on behalf of Covid-19 Working Group of Indian Society of Nephrology

Organ transplant recipient are at a risk for more severe COVID-19 if they get SARS CoV-2 viral infection. Further, there is potential risk of infection transmission through the donor to recipient through organ transplantation. Further, there are issues in recipient and donor selection for transplant. In view of these issues' organ transplant at the time of COVID-19 pandemic should be undertaken with caution and should be done only at the centre where facilities of treatment of COVID-19 patients are available.

1. The pre, peri and post-transplant areas, including the operation theaters need to be specifically ear marked for this purpose.
2. Staff involved in their care may not be involved in care of other patients.
3. There has to be adequate availability of PPE specifically ear marked for their care
4. The center should not be one earmarked for the treatment of COVID-19 patients and

needs to have protocols for patient movement around the hospital to prevent nosocomial acquisition of COVID

1. DeceasedDonors

Following individuals, who are potential deceased donor should NOT be accepted as deceased donors:

Epidemiological criteria –

- International travel in the 14 days before illness onset or close to it

- Contact in 14 days before illness onset with a confirmed case of COVID-19 or healthcare worker with direct patient contact

Clinical criteria – Where the cause of death was due to unexplained respiratory failure or where there was history of Fever OR Acute respiratory infection (e.g. shortness of breath, cough, sore throat) with or without fever.

Exclude as deceased donors:

- If confirmed Covid-19 positive – do not work up for donation if known infection; stand down case if positive result obtained as part of donor workup.

- If COVID-19 is suspected due to presence of severe bilateral community-acquired

pneumonia and no other cause is identified (irrespective of COVID-19 PCR test results)

Routine testing of deceased donors

Routine COVID-19 (SARS-CoV-2) viral testing should be undertaken in all deceased donors, with results obtained before proceeding with donation in specific circumstances as described below. Testing should occur within the 72 hours prior to donation.

Tests required are:

- Nose and throat swab (PCR test)
- Blood tube (for retrospective serology testing)

Where possible obtain the PCR results prior to proceeding with donation.

NOTE: Testing of donors is solely for the purpose of improving safety in transplantation and does not infer any suspicion of COVID-19 infection in these patients.

Unless COVID-19 is suspected on epidemiological or clinical grounds, additional precautions to those usually employed for acquiring respiratory samples in standard, non-COVID-19 intensive care patients are NOT required. Specifically, there is no need for patient isolation or the use of non-standard ICU PPE in ongoing care of these patients.

2. Living relatedTransplants

The living donor transplant programme may be temporarily suspended in line with the MoHFW's Advisory for Hospitals and Medical Institutions dated 03-03-2020, accessible at https://www.mohfw.gov.in/pdf/AdvisoryforHospitalsandMedicalInstitutions.pdf

However, if transplant is being done, following individuals, who are living donor should NOT be accepted as donors:

a. Individuals who have been exposed to a confirmed or suspected COVID-19 patient within the last 14 days

A suspected case is a patient satisfying epidemiological AND clinical criteria:

Epidemiological criteria –

- International travel in the 14 days before illness onset or close to it

- Contact in 14 days before illness onset with a confirmed case of COVID-19 or healthcare worker with direct patient contact

Clinical criteria – Fever OR Acute respiratory infection (e.g. shortness of breath, cough, sore throat) with or without fever.

Note that these criteria are current as of the date of writing this document and

may change with up-to-date recommendations.

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RT-PCR test of potential donors with suspicion of COVID-19 should be undertaken as suggested for deceased donors

3. Emergency lifesaving Transplantation

In case a transplant is to be done in an acute emergency setting, it should be performed with appropriate assessment and evaluation of COVID-19 infection in the donor as well as in the recipient. Appropriate counseling of both the donor and recipient as well as their families should be done, and a high-risk informed consent taken before proceeding with thetransplant.

A rigorous epidemiological survey should be conducted among potential donors and their family's members.

4. TransplantationRecipients

Similar to the general population, transplant recipients should also strictly follow the travel advisories issued by the various ministries of Government of India from time to time. They should take extra precaution as they have risk of developing severe COVID-19 disease.

5. 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 centres. All transplant centres must have guidelines in place specifying which patients need testing and inpatient management and which patients can stay at home with close telephonic follow up.

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 present to the nearest emergencydepartment.

6. Treatment and modification ofimmunosuppression

There are two issues of management of organ transplant patients with COVID-19

a. Management of COVID-19 in transplant patient.

There is scarcity of data and consensus on effective treatments of COVID-19 in transplant patients. Few centres 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

Foods and Drug Administration (FDA) for COVID-19.

b. Management of organ transplant 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 overall agreement of stopping antimetabolite drugs and decrease calcineurin inhibitors by 50%. Steroid should be continued on same doses. (Massachusetts General Hospital COVID-19 Treatment Guidance).

7. Post-transplant follows up measures

Transplant patients are at risk for severe COVID 19 if they acquire infection due to immunosuppressed state. They may not manifest symptoms like general population. Fever may be absent as reported from study from China. Transplant units are advised to consider ways to limit hospital attendance for patients, such as:

1. rescheduling non urgent 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

8. <u>TissueTransplantation</u>

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

Tissue and Eye Donation Criteria:

▪ 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, deferral will be based upon exposure in the last 28 days before donation:

- Close contact with a person who has confirmed COVID-19 infection
- Close contact with a Person under Investigation (PUI) for COVID-19
- International travel

9. Personnel Precautions working in the program :

The health and safety of all the working in the transplant program is of paramount importance. A number of retrieval and transplanting staff have raised concern regarding their personal risk of contracting COVID 19 during surgery.

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.

In case of donation or transplantation -

▪ Personnel should follow all hospital-based protocols for the isolation and management of COVID-19 patients.

▪ 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.

▪ 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 be documented clearly and accurately. Documentation should include transmittable disease status, COVID-19 testing status/high risk suspicion and/or individual organ suitability.

▪ Screening questions should reflect updated COVID-19 national guidelines

- .Please refer to below links for moreinformation:-

  - 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-coronavirus-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-coronavirus-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 officialcorrespondence on23-03-2020.

Disclaimer:

The current outbreak is unpredictable. If widespread community-transmission occurs, healthcare infrastructure and capacity issues may have further impact on donation and transplantation. These recommendations will be regularly updated to account for the changing epidemiology and new information regarding 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

25th March, 2020

Chapter-6:

Anti-corona vaccines and drugs - current scenario

Edwin Fernando, Sishir Gang, and Arpita Roy Chaudhary on behalf of Covid-19 Working Group of Indian Society of Nephrology

In late December 2019, an outbreak of an emerging disease (COVID-19) due to a novel coronavirus (named SARS-CoV-2 latter) started in Wuhan, China, and rapidly spread in China and outside. The WHO declared the epidemic of COVID-19 as a pandemic on March 12th 2020. The overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to79 years and 14.8% in those aged >80 years.

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.

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.

Numerous collaborative efforts to discover and evaluate effectiveness of antivirals (eg, remdesivir), immunotherapies (eg,hydroxychloroquine, sarilumab), monoclonal antibodies, and vaccines have rapidly emerged

ANTIVIRAL THERAPY

Lopinavir/Ritonavir

The guidelines of the Chinese National Health Commission recommend aerosolized inhalation of interferon and lopinavir/ritonavir. (1)

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 rangeof ventilatory support modes (eg, 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.(2)

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.(3)

Remdesivir

The broad-spectrum antiviral agent remdesivir (GS-5734; Gilead Sciences, Inc) is a nucleotide analog prodrug. Several phase 3 clinical trials are underway for testing remdesivir for use in COVID-19 in the United States, South Korea, and China.

An in vitro study showed that the antiviral activity of remdesivir plus interferon beta (IFNb) 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-IFNb slightly reduced viral loads without affecting other disease parameters. Therapeutic LPV/RTV-IFNb improved pulmonary function but did not reduce virus replication or severe lung pathology (4)

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.

Chloroquine

Chloroquine phosphate has been shown to have some efficacy against COVID-19–associated pneumonia in multicenter clinical trials conducted in China.(5)

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(6)

Wang et al reported that chloroquine effectively inhibits SARS-CoV-2 in vitro.(7)

On 20th March 2020, ministry of health and family welfare have suggested the use of chloroquine in the following circumstances

1. Asymptomatic health care workers involved in the care of suspected or proven cases of COVID -19
2. Asymptomatic household contacts of laboratory confirmed cases

The recommendations are not evidence based. Further, this should not instill a sense of false security. They must continue to follow the preventive norms and behaviour as suggested by local health authorities.

Glucocorticoids

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.(8)

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.(9)

In a meta-analysis of corticosteroid use in patients with SARS, 4 studies provided conclusive evidence of harm (psychosis, diabetes, avascular necrosis, and delayed viral clearance).(10)

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.(11)

Convalescent plasma.

Preliminary clinical studies in China have shown that early application of convalescent plasma in patients with COVID-19 could accelerate clinical recovery.(12)

Currently 2 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, are underway in China.

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.(13)

Tocilizumab, a monoclonal antibody against the IL-6 receptor, has achieved encouraging preliminary clinical results.

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 600mg 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. Presence and absence of 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)

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.

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Chapter-6:

Infection Prevention and Control Guidelines for COVID

Sandip Mahajan, HS Kohli, Manish Rathi, and KL Gupta onbehalf of Covid-19 Working Group of Indian Society of Nephrology

The best way to prevent corona virus disease 2019 (COVID-19) is to avoid exposure to the virus. There is currently no effective vaccine to prevent COVID. With the information available currently, the main route of spread is person-to-person, either from a symptomatic affected person or from an asymptomatic carrier, via respiratory droplets or contact. 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 epidemic. The following recommendations apply for all general public in addition to patients with chronic kidney disease.

General Advice

- Avoid agglomerations and closed crowded spaces.
- Maintain a distance of at least 1 – 2 meters especially from persons with respiratory symptoms.
- Stay home if sick or with any respiratory symptoms or even if asymptomatic, if there is contact with a suspected COVID patient.

- Avoid non-essential travel.

Hand hygiene

- Wash hands with soap and water for at least 20 seconds especially after blowing your nose, coughing, sneezing or being in any public place.
- If hand is not soiled and/or soap is not available, use a hand sanitizer with at least 60% alcohol.
- “My 5 moments for hand hygiene” are a simple effective guide on how to perform hand hygiene.
- If soap or alcohol-based hand rub is not available, chlorinated water (0.05%) can be used – Repeated use may lead to dermatitis and should be watched out for.
- Refrain from touching your eyes, nose and mouth with unwashed hands.
- Dry hands with a clean, dry cloth, single-use towel or hand drier as available.

Respiratory etiquette

- Cover the nose and mouth with a tissue when you cough or sneeze or use the inside of your flexed elbow. The tissue has to be disposed in the trash immediately.
- Immediately wash your hands with soap and water or use a hand sanitizer as advised earlier.

Face mask

- Use a facemask only when you have respiratory symptoms, you care for those with respiratory symptoms or when entering a healthcare provider’s place.
- Facemasks are required for caregivers and healthcare providers
- Do not use facemasks if there is no indication.
- A triple layered surgical mask is sufficient for personal protection.

Masks management

- Mask has to cover mouth and nose minimizing all gaps between the mask and face
- Do not touch the mask when in use.
- Remove masks by removing the lace from behind. If in contact with front of the mask / damp mask – perform hand hygiene and replace the mask
- Do not re-use single-use masks
- If face masks are not available, homemade masks like scarfs can be used as a last resort and it should cover the entire front and sides of the face and should extend to the chin or below.

General Cleaning

- Like other coronaviruses, COVID-19 can survive on surfaces for 2 hours to 9 days depending on a number of environmental factors.
- Clean frequently used objects / surfaces daily – phones, tablets, handles, keyboards and switches, etc.
- 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.
- List of household detergents effective against COVID-19 are available in https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2.
- Cleaning with soap and water can be done if surfaces are dirty.
- 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.

Water supply

- Though COVID-19 has not been yet detected in drinking water, like other coronaviruses chlorination and disinfection with ultraviolet light as done in conventional, centralized water treatment methods should be effective.
- If centralized supply is not available, household water treatment methods including boiling, using nanomembrane filters, chlorine or UV irradiation may be used.

Chemoprophylaxis

The National task force for COVID-19 by ICMR has recommended use of hydroxy-chloroquine for prophylaxis in high-risk population viz. asymptomatic health-care workers involved in care of suspected/confirmed case of COVID-19 and asymptomatic household contacts of confirmed cases. The doses recommended are 400 mg twice a day on day 1 followed by 400 mg once a week for 7 weeks for health care workers and 400 mg twice a day on day 1 followed by 400 mg once a week for 3 weeks for asymptomatic household contacts of confirmed cases.

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