

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 other 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.^[3] 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]

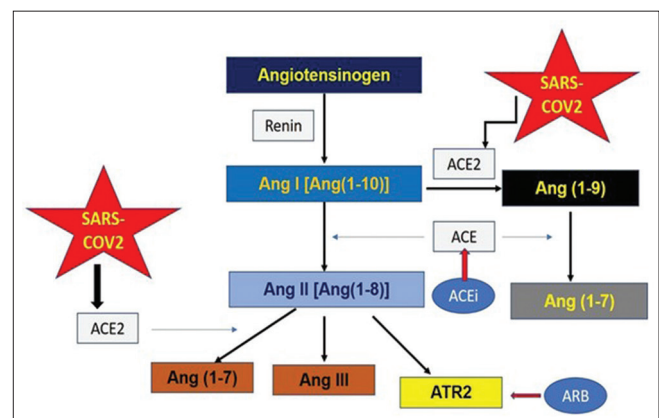


Figure 1: Interaction between RAAS, SARS-COV2 and angiotensin converting enzyme inhibitors and angiotensin II receptor Blockers

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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References

1. Ma Y, Diao B, Lv X, Zhu J, Liang W, Liu L, et al. 2019 novel coronavirus disease in hemodialysis (HD) patients: report from one HD center in Wuhan, China. MedRxiv 2020. doi: 10.1101/2020.02.24.20027201.
2. Telemedicine Practice Guidelines: Enabling Registered Medical Practitioners to Provide Healthcare Using Telemedicine. Available from: <https://www.mohfw.gov.in/pdf/Telemedicine.pdf>. [Last accessed on 2020 Mar. 25].
3. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med 2020. doi: 10.1056/NEJMs2005760.
4. Sommerstein R. Preventing a covid-19 pandemic. BMJ 2020;368:m810.
5. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. Lancet Respir Med 2020;8:e21.
6. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. China CDC Weekly 2020;2:113-22.
7. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020;ehaa235. doi: 10.1093/eurheartj/ehaa235.
8. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of ACE 2 in SARS Corona-virus induced lung injury. Nat Med 2005;11:875-79.
9. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 2020. doi: 10.1002/ddr.21656.
10. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. doi: 10.1093/cid/ciaa237.
11. Gautreta H, Lagiera JC, Parolaa P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020. doi: 10.1016/j.ijantimicag.2020.105949.
12. Ministry of Health and Family Welfare [Internet]. Government of India. Advisory on the use of Hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. 2020 [cited 2020 March 22]. Available from: <http://www.mohfw.gov.in>. [Last accessed on 2020 Apr 19].

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