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## Review Article

## Kidney involvement in COVID-19 and potential treatment opportunities

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## ABSTRACT

Connection between direct kidney involvement and novel Coronavirus Disease (COVID-19) has been less evident until now. In today's critical scenario of COVID-19, as healthcare professionals, our prime responsibility is to create awareness in clinician and general public as to mysterious facts of kidney involvement in Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2). Further, we have shed light on the clinical management of patients with chronic kidney disorders, particularly those on dialysis and having kidney transplants who are critically ill with COVID-19. Based upon our comprehensive literature review, we concluded that kidney involvement is an independent risk factor for mortality in patients with COVID-19 infection. This paper will assuredly be helpful for the new generation nephrologists to deal with such a disastrous situation.

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## 1. Review

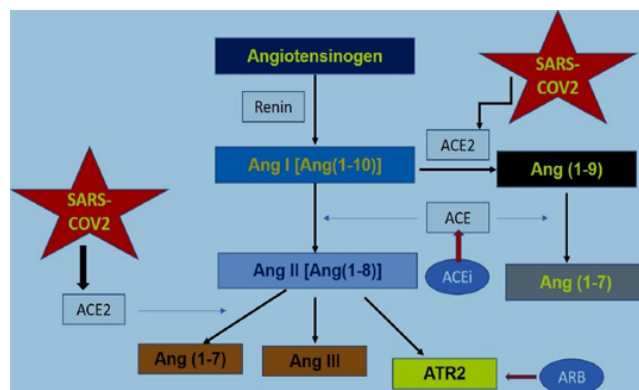
CoronaVirus Disease 2019 (COVID-19) is referred to as an illness caused by a novel corona virus now termed as Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first recognized amid an outbreak of respiratory illness victims in Wuhan City, Hubei Province, China.<sup>1</sup> On 11 March 2020, the World Health Organization (WHO) proclaimed novel COVID-19 to be a global pandemic.<sup>2,3</sup> As of 28 April 2020, COVID-19 has been confirmed in more than 3 million individuals worldwide and resulted in more than 2,12,000 deaths. From all continents, more than 180 countries have reported laboratory-verified cases of COVID-19 except Antarctica.<sup>4</sup> The incubation time in the beginning stages was 5.2 days, with the epidemic size doubling every 7.4 days<sup>5</sup>, thereby showing a high risk of human-to-human transmission. Transmission routes involved droplet inhalation transmission, direct

transmission through coughing and sneezing, as well as contact transmission, including oral, nasal, and eye mucous membrane contacts. Of the many human-pathogenic corona viruses, most of the viruses presented with mild clinical symptoms; with two notable exceptions: Severe Acute Respiratory Syndrome Corona virus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The first one was the novel beta coronavirus that appeared in November 2002 in Guangdong, Southern China and another was first detected in Saudi Arabia in 2012 and, then, also observed in South Korea. Both of these variants are associated with a high rate of mortality. What we have found so far is that the genomic analysis of SARS-CoV-2 showed remarkable phylogenetic divergence from previously known corona viruses that caused human disease.<sup>6</sup> Even though of these differences, multiple documented studies have stated that SARS-CoV-2 utilizes the identical membrane-bound Angiotensin-Converting Enzyme 2 (ACE2) as SARS-CoV for entry to its target cells<sup>7,8</sup>, however, of interest the matter is that it

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has a higher binding affinity.<sup>9</sup>



**Fig. 1:** Interaction between RAAS, SARS-COV2 and ACEi/ARB<sup>10</sup>

ACE2 is a carboxypeptidase that especially removes carboxy-terminal hydrophobic or basic amino acids. It acts as a receptor for both SARS-CoV-1 and SARS-CoV-2 viruses which result in the interaction between Renin-Angiotensin-Aldosterone System (RAAS) and SARS-CoV.<sup>11</sup> COVID 19 viral S protein gains entry into the target cells by binding with surface ACE-2 of the cardiopulmonary cells. The ACE2 is mainly contributed to the degradation of Ang II, which in turn, leading to the synthesis of angiotensin I-VII which opposes the effects of Ang II. With the use of ACE inhibitors/angiotensin receptor blockers (ACEi/ARBs), the expression of ACE-2 receptors may be elevated (Figure 1).<sup>10</sup> These patients may have significant risk of infection as the increased number of the receptor are available.<sup>12,13</sup> In light of existing evidence, higher mortality is associated with old age and other co-morbidities such as hypertension, diabetes, cardiovascular disease<sup>14</sup>, hence, a question raised, whether the use of ACEi/ARBs, which is widespread in these subgroup of patients, may increase the risk and possible threat to COVID-19 infection. There has been no shred of evidence that indicates the mortality associated with ACEi/ARBs use in the patients of COVID-19.

Data extracted out from normal lung tissue and two single-cell transcriptomic datasets revealed that ACE2 gene expression was not significantly associated with ethnicity (Asian vs. Caucasian), age (>60 vs. < 60) and sex (male vs. female).<sup>15</sup> A recent study by Zumla et al.<sup>16</sup> reported that ACE2 is highly expressed in the mouth as well as tongue, which promotes viral entry in the host. In normal human lung, it has also been localized in lower lungs on type I and II alveolar epithelial cells. After infection, the entry of SARS-CoV-2 begins with the binding of the spike glycoprotein expressed on the viral envelope to ACE2 on the alveolar surface resulted in stimulation of the clathrin-dependent endocytosis of the whole SARS-CoV-2 and ACE2 complex, provoking fusion at the cell

membrane. This endosomal cell entry of SARS-CoV-2 is aided by a low pH and pH-dependent endosomal cysteine protease cathepsins. Once entered in the cells, SARS-CoV-2 utilizes the endogenous transcriptional system of the alveolar cells to replicate it and spreads throughout the entire lung. Besides, it is also expressed in kidney, heart as well as enterocytes in the gut.<sup>17</sup> Whether robust evidence for ACE2 expression in these organs affected by SARS-CoV-2 infectivity remains ill-defined. Lung involvement is the frequently appeared manifestation among documented cases of SARS-CoV-2, and shred of evidence has been available on this matter. However, kidney involvement is also predicted with this condition, however, robust evidence are still lacking.

Before starting in regards to kidney involvement, we would explore the mechanisms of kidney injuries by COVID-19. This mechanism seems to be multifactorial and, still, it is obscure.<sup>18</sup> The direct viral cytopathic effect on kidney tissue is an assumed mechanism, which is backed by the verdict of viral nucleic acid material of coronavirus in blood and urine in SARS-CoV as well as COVID-19 patients.<sup>19,20</sup> As mentioned earlier, the molecular study proved that coronavirus uses ACE2 receptor for cell entry in the same manner as SARS-CoV. ACE2 and Dipeptidyl Peptidase-4 (DPP4), both expressed on renal tubular cells, were recognized as binding partners for SARS-CoV and MERS-CoV, respectively. In fact, ACE2 expression is 100-fold higher in kidney tissues as opposed to lung.<sup>21</sup> It directly hints that ACE2 dependent pathway may be used by coronavirus to infect kidneys more severely than the lung. There are, nevertheless, clinical investigations are distinct from this, which stated more lung involvement than kidney. Another presumable mechanism may be the direct effector T cell-mediated injury and immune complex-mediated glomerular injury with viral antigen and specific antibody. However, this hypothesis is contraindicated with the existing evidence showing normal glomerular aspect on microscopy and absence of electron-dense deposit in SARS-CoV patients.<sup>22</sup> Inducing sepsis and cytokine storm theory are others possible explanation.<sup>23</sup> The cytokines and other mediators are released after coronavirus infection contribute to a sustained inflammatory response which, in turn, resulted in hypotension, hypoxia, shock, and target organ injuries. Clinical pictures of COVID-19 patients with sepsis somehow backed by this concept. The indications are especially severe, with a variety of signs and symptoms of multiorgan involvement. These signs and symptoms include respiratory events like severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs presented as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia. However, these outcomes propose the presumable mechanism of Acute Kidney Injury (AKI) in many terminal cases. Wang

et al.<sup>24</sup> revealed that there was a trend for elevated creatine kinase levels in 138 patients with COVID-19 disease admitted into intensive care units. It indirectly leads to AKI through the effects on renal tissues, due to hypotension, hypoxia, shock, and rhabdomyolysis. As well, these patients may progress kidney injuries otherwise.

Existing data suggested that AKI, cardiac damage and abdominal pain are the most prevalent co-morbidities of COVID-19 indicate that SARS-CoV-2 may have a tropism for these organs.<sup>25,26</sup> None the less replication of SARS-CoV-2 actually occurs in these organs, potentially have impact on their functional homeostasis and lead to virus spreading throughout the body remains more disputing matter. In agreement with Ye et al.<sup>27</sup>, in the kidney, ACE2 is profoundly expressed in the brush border of proximal tubular cells and, to a lesser amount, in podocytes, however absent in glomerular endothelial and mesangial cells. Historical data obtained from the SARS outbreak in 2003 revealed that only 6% of SARS-CoV-infected patients were associated with AKI. Even though it was a relatively unusual feature of this condition, AKI was recognized as a lethal complication of SARS, because around 92% of SARS cases with AKI died.<sup>22</sup> Chu and co-workers<sup>22</sup> endeavored to assess whether AKI was triggered by active SARS-CoV replication in tubular cells that express a higher amount of ACE2, for that renal specimen were collected from post-mortem SARS patients with AKI and evaluated for the presence of SARS-CoV viral particles using electron transmission microscopy. They further pronounced that SARS-CoV was not identified in any of the investigated patients and asserted that kidney dysfunction was potentially associated with multi-organ failure. Moreover, they postulated that AKI in SARS patients might occur on account of specific pathogenic conditions, include cytokine release syndrome rather than active viral replication in the kidney. Assuredly, growing viral infection in alveolar cells triggers gross recruitment of immune cells which generate a large extent of cytokines, inducing multiple organ failure. Later on, these findings were supported by Huang et al.<sup>28</sup>, who stated that an interferon-gamma-related cytokine storm was provoked post-SARS-CoV, resulted in severe organ damage in SARS victims. This concept is not new to nephrologists because inflammatory AKI has been documented under many clinical conditions like immune-checkpoint inhibitors<sup>19</sup> and chimaeric antigen receptor (CAR) T cells in cancer patients and thyroglobulin treatment in kidney transplanted patients.<sup>29</sup> According to Dio et al.<sup>30</sup>, the human kidney is a specific target for SARS-CoV-2 infection. They further investigated viral nucleocapsid protein in situ in the kidney post-mortem and determined that SARS-CoV-2 antigens accumulated in kidney tubules, hints that SARS-CoV-2 infects the human kidney directly, causing AKI and offers viral spreading in the body. The contrast among the higher

renal tropism of SARS-CoV-2 vs. SARS-CoV might be justified by the enhanced affinity of SARS-CoV-2 for ACE2, permitting more prominent kidney infection, which may serve as a viral reservoir.<sup>31</sup> Some studies reported that proteinuria and haematuria are the typical clinical manifestations evident in almost 40% of total admitted cases in hospital.<sup>32</sup> Moreover, elevated level of blood urea nitrogen and serum creatinine are also noted. The kidneys CT scan displays decreased density is suggestive of inflammation and oedema. Thus, this study emphasizes on renal impairment as an independent predictor of mortality. Moreover, patients infected with SARS-CoV-2 appear to be affected by AKI most commonly than those infected with SARS-CoV. In the Indian scenario, in 2020, due to corona the incidence of AKI has been observed in 5.1% of total cases and presumably, half of them may need renal replacement therapy.<sup>18</sup> Recently, Yao et al.<sup>33</sup> hypothesized that SARS-CoV-2 infection damages not only lungs but vessels, kidney and other organs as well. Further, hyaline thrombi are detected in small vessels in various organs. Detail investigation of physiological changes in autopsy content would be of utmost importance. It is fact that cytokine release syndrome is also a characteristic of SARS-CoV-2 infection, which resulted in AKI, yet this still remains a mysterious matter. As yet, a specific inhibitor of interleukin 6 (IL-6), the leading driver of cytokine release syndrome, appears to be beneficial in severe condition.<sup>26</sup> With increased stage and severity of AKI, the hazard ratio of death for COVID-19 patients also increases.

The computed epidemiological data have indicated that AKI is one of the leading risk factors in COVID-19 prognosis and diabetes is the prime kidney co-morbidity, yet the influence of other kidney diseases like end-stage kidney disease and transplantation is still not evident at this stage of the pandemic. Given the fact that higher incidence of SARS-CoV-2 infection in hospitalized patients, COVID-19 patients demonstrates critical challenges for patients on dialysis. In haemodialysis patients, the course of the disease outbreak was observed at Renmin Hospital in Wuhan University during January 14, 2020, to February 17, 2020. During the epidemic, 230 haemodialysis patients were admitted and from which 37 patients had COVID-19 infection. Finally, seven haemodialysis patients died, including six with COVID-19 and one without COVID-19.<sup>34</sup> The causes of death were not linked with pneumonia. In haemodialysis patients infected with SARS-CoV-2, biochemical estimation of peripheral blood samples was performed and achieved findings revealed a significant decline in the amounts of T cells, T helper cells, killer T cells, and natural killer cells in human peripheral blood mononuclear cells, as well as lower serum levels of inflammatory cytokines as compared to non-haemodialysis patients with COVID-19. Additionally, this review concluded that haemodialysis

patients with COVID-19 were expected to experience mild disease that did not develop into full-blown pneumonia, potentially due to diminished immune system activity and decreased cytokine storms. Moreover, this article also postulated higher risk of SARS-CoV-2 infection in haemodialysis patients and, further preventive measures are necessary in treating COVID-19 in haemodialysis centres. Recently, The Chinese Society of Nephrology and the Taiwan Society of Nephrology have established more comprehensive guidelines for managing COVID-19 outbreaks in dialysis units.<sup>35</sup> Also, Indian society of Nephrology-COVID 19 working group has formulated the guidelines/suggestions for the management of COVID in patients with a kidney disorder.<sup>10</sup>

Currently, the management of COVID-19 with AKI involves a conservative approach with sufficient hydration, nutritional support, and paracetamol with the aim of the self-recovery of the patients in the quarantine. The patient with respiratory distress may require oxygen therapy and intensive care with ventilator support in case of SARS. An N95 fit-tested respirator as well as, protective clothing and equipment are most essential for patients and, the caregiver should also use appropriate protective masks and clothes. In absence of effective antiviral therapy, the most comprehensive prospective research on AKI with COVID-19, three medicines including, antivirals (73.0%), antibiotics (71.0%), and glucocorticoid (36.9%) are mostly used. Anti-virals demonstrated mortality benefit, and glucocorticoids did not, which is likely due to physician are used steroid only in cases which were terminally ill. Different types of anti-viral were used, including arbidol hydrochloride, ganciclovir, interferon, lopinavir, ritonavir, oseltamivir, ribavirin and remdesivir, which resulted in no significant difference between patients with AKI and those without AKI.<sup>18</sup> The randomized controlled trial reported by Cao et al.<sup>36</sup> hypothesized that no mortality benefit (19.2%) compared to the standard of care arm (25%) was reported with the treatment of lopinavir-ritonavir. Moreover, the median time of clinical improvement was only one day shorter in the treatment arm. As a consequence, lopinavir-ritonavir treatment was stopped early in 13.8% of cases due to adverse events. Remdesivir is a nucleotide analogue with in vitro activity against SARS-CoV-2. It has shown to reduce recovery time<sup>37</sup> hence, Infectious Disease Society of America (IDSA) and National Institutes of Health (NIH) suggest the use of remdesivir in patient who requires low flow oxygen supplementation. The United States Food and Drug Administration (USFDA) has approved remdesivir for all adult with COVID-19 regardless of severity.<sup>38</sup> The pharmacokinetics of remdesivir in the setting of renal impairment are uncertain, and it is prepared in a cyclodextrin vehicle that accumulates in renal impairment and may be toxic; thus, remdesivir is not recommended in patients with an estimated glomerular filtration rate

(eGFR) <30 mL/min/1.73 m<sup>2</sup> unless the potential benefit outweighs the potential risk. Given the short duration of therapy and the low concentration of the cyclodextrin vehicle, the risks in patients with renal impairment may be relatively low. A case series from India have reported safe use of remdesivir in patients with AKI and chronic kidney disease (CKD).<sup>39,40</sup> Liver enzymes should be checked before and during remdesivir administration; alanine aminotransferase elevations >10 times the upper limit of normal should prompt consideration of remdesivir discontinuation.<sup>41</sup> Favipiravir has been extensively utilized in India in mild infection but supporting evidence are still not satisfactory.

In a clinical trial conducted in china, chloroquine phosphate demonstrated some efficacy against COVID-19 associated pneumonia<sup>42</sup>, however it is not showed clinical improvement in real word patients, hence currently it is not prescribed. Initial over exacerbated use of prophylactic hydroxychloroquine is now reduced due to poor efficacy and inadequate data.

Glucocorticoids like dexamethasone or equivalent steroids have been advised in patients with hypoxia or ventilatory support. Accumulated evidence suggests the benefits of glucocorticoids in treating COVID-19. They also concluded that glucocorticoids are associated with reduction in mortality and requirement of mechanical ventilation. By contrast, a benefit was not observed among patients who did not require either oxygen or ventilatory support; there was a no statistically significant trend towards higher mortality.<sup>43,44</sup>

The use of convalescent plasma has been attempted for early phase of disease particularly for the patients who are deficit in immunoglobulins, however a lack of evidence based data in case of severity of COVID-19. A monoclonal antibody against the IL-6 receptor such as Tocilizumab and sarilumab have been endeavored in patient who required intensive treatment and has rapid progression with early presentation (within 24-48 hours) of disease and elevated inflammatory bio markers (CRP > 75 mg/L, ). It shows some benefits in this subset of patients.<sup>45-48</sup>

Baricitinib, Janus Kinase inhibitor has been utilized in combination with remdesivir in patients who require oxygen therapy and ventilatory support, who are having contraindication for glucocorticoid use.<sup>49</sup>

Interferons modulate immune responses and may have antiviral effects. Interferon beta, specifically, has been reported to inhibit SARS-CoV-2 replication in vitro.<sup>50</sup> Overall, clinical data do not indicate a clear benefit of interferon beta for severe COVID-19. A monoclonal antibody directed against the RAAS-binding domain of the S- protein of MERS-CoV is under investigation and reports are awaited.

Based on the mechanism of kidney injury by a coronavirus, extracorporeal therapy is also proposed in the

**Table 1:** Potential mechanism of kidney damage and treatment approaches in COVID-19<sup>51</sup>

<b>Pathway</b>	<b>Mechanism of kidney damage</b>	<b>Proposed treatment approach</b>
Cytokine damage Cytokine release syndrome Increased cytokine generation owing to extracorporeal membrane oxygenation, invasive mechanical ventilation and/or continuous kidney replacement therapy	Direct cytokine lesion	Removal of cytokine by: direct haemoperfusion using a neutro-macroporous sorbent; plasma adsorption on resin after separation from whole blood; continuous kidney replacement therapy with hollow fibre filters with adsorptive properties; high-dose continuous kidney replacement therapy with medium cut-off or high cut-off membranes
Haemophagocytic syndrome Organ crosstalk Cardiomyopathy and/or viral myocarditis	Cardiorenal syndrome type 1	Left ventricular assist device, arteriovenous extracorporeal membrane oxygenation
Alveolar damage	Renal medullary hypoxia	Venovenous extracorporeal membrane oxygenation
High peak airway pressure and intra-abdominal hypertension	Renal compartment syndrome	Venovenous extracorporeal membrane oxygenation, extracorporeal CO <sub>2</sub> removal, continuous kidney replacement therapy
Rhabdomyolysis	Tubular toxicity	Continuous kidney replacement therapy using a high cut-off or medium cut-off membrane
Systemic effects Positive fluid balance	Renal compartment syndrome	Continuous ultrafiltration and diuretics
Endothelial damage, third-space fluid loss and hypotension	Renal hypoperfusion	Vasopressors and fluid expansion

case of severity (Table 1).<sup>52</sup>

Many patients of CKD will experience episodes of AKI after COVID-19 infection, and the renal function will deteriorate after infection leading to acute kidney disease. Such a decline in kidney function depends on the severity of the infection. For the management of CKD, multiple pills for hypertension (Mainly: calcium channel blockers, centrally acting drugs like clonidine, beta-blockers, alpha-blockers, and ACEi/ARB), metabolic bone disorders (MBD), and anaemia are recommended. Therapy for anaemia and CKD-MBD should be continued as before the COVID 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 in CKD. CKD patients with COVID infection should avoid taking NSAIDs and instead should take paracetamol as there are unconfirmed reports of patients who are on NSAIDs having more severe disease compared to acetaminophen/paracetamol.

We have previously mentioned that there is in general riddle about the use of ACEi/ARB in COVID-19 patients. In response to this doubt, we suggest continuing ACEi and ARBs for anti-hypertensive and renoprotective purposes as

well as any other hypertensive drugs also. Then, the second question is rising in mind "Why we can use"? This can be explained by the high angiotensin II (in severe cases or the absence of ACEi/ARB) could open up the ACE-2 receptor by unbinding of ATR-1, thereby making it available for COVID-19 to attach. These conclusions propose 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.<sup>14</sup>

CKD-5 patients on dialysis [maintenance hemodialysis (MHD) or continuous ambulatory peritoneal dialysis (CAPD)] are also vulnerable group due to their existing comorbidities, repeated unavoidable visit to the hospital environment and immunosuppressed state due to CKD-5. Therefore, these patients are more prone to the acquire infection as well as also progress severe diseases as opposed to the general population.

In dialysis managing settings, timely recognition and isolation of patients affected with a respiratory infection, patient placement and the usage of individual protective devices are the key priority. Further, the dialysis unit should have a designated screening area, where patients can be

screened for COVID-19 before allowing them to enter inside the dialysis area.

At the end, the probability of getting COVID-19 from organ donation is low. SARS-CoV-2 has been displayed to replicate in approximately 30% of COVID-19 patients.<sup>52</sup> Because of this reason, screening for COVID-19 in kidney donors should also be major issues. The main criteria for deceased-donor are mentioned as followings:

1. International travel in the last 14 days before the onset of current event leading to brain stem death
2. 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 healthcare worker with direct patient contact
3. Where the cause of death was due to unexplained respiratory failure
4. Where there was a history of fever or acute respiratory infection (e.g., shortness of breath, cough, sore throat) with or without fever.
5. Severe bilateral community-acquired pneumonia in the absence of any other cause
6. Confirmed Covid-19 positive case or test found positive while donor workup is being done

RT-PCR test of potential donors should be undertaken as suggested for deceased donors. Few centers have researched on anti-virals, 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. 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 organ rejection. However, there is an overall agreement of stopping anti-metabolite drugs and decrease calcineurin inhibitors by 50%. Transplant patients are at risk for severe COVID-19 if they acquire infection due to their immunosuppressed state. They may not manifest symptoms like general population. Fever may be absent as reported in the 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 tele medicine 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.

## 2. Source of Funding

None

## 3. Conflict of Interest

None.

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