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The Kidney and COVID-19

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes coronavirus disease 2019 (Covid-19), appears to be more severe in patients with chronic illnesses, including those with chronic kidney disease (CKD) [1,2] putting them at higher risk of complications and of dying. Many innovative therapeutic approaches continue to be studied for the treatment of severe Covid-19 [3]; attention has also been directed, appropriately so, in screening high-risk patients and employing preventative strategies to reduce the spread of the virus, especially in dialysis units due to inherent challenges in maintaining social distancing [4]. Dialysis patients with Covid-19 may present with less classic clinical manifestations such as diarrhea [5] in addition to fever and fatigue, making it important for health care providers to have a high index of suspicion for this infection in patients receiving dialysis.

In addition to the higher morbidity seen in patients with CKD patients, there are several other kidney-related implications of Covid-19 that nephrologists need to be aware of. These include the risk of developing acute kidney injury (AKI) in the setting of severe infections, reports of heavy proteinuria and collapsing focal segmental glomerulosclerosis (FSGS) in patients with Covid-19 and the debate about the safety of angiotensin-converting enzyme (Ace) inhibitors and angiotensin receptor blockers (ARBs) in patients with Covid-19.

AKI in Covid-19

Not surprisingly, patients with severe Covid-19 can develop multi-organ failure, including AKI and this is more common in the setting of pre-existing co-morbidities (2). While the initial reports from China suggested a low incidence of AKI, recent data suggest otherwise; incidence rates as high as 10%-15% have been seen, with some patients needing continuous renal replacement therapy (2).The incidence of AKI is significantly higher in patients with elevated baseline serum creatinine than in patients with normal baseline values. In addition, the development of AKI during hospitalization is associated with a higher incidence of in-hospital mortality [6], which is similar to what has been seen with any other etiology of AKI. Interestingly, data from Chinese patients showed a surprisingly high incidence of proteinuria (44%) and hematuria (27%) on admission in patients with Covid-19, which might indicate other mechanisms of renal injury, unrelated to systemic inflammation, as will be discussed below.

Glomerulopathy

As mentioned above, a large proportion of hospitalized patients with Covid-19 have, on admission, heavy proteinuria and hematuria; the prevalence of proteinuria has been reported to increase even further during hospitalization [7]. Interestingly there are 2 case reports [8,9] of patients with Covid-19 developing collapsing FSGS. On the renal biopsy specimen, no significant inflammatory infiltrate was seen in either patient. In one patient no viral RNA could be extracted from the tissue; however viral like particles were noted on electron microscopy [9]. In the other [8], viral antigen was detected in the renal tubules on immunohistochemistry.

This indicates that the etiology of renal involvement in patients with Covid-19 is likely multifactorial and in some patients the virus may exert a direct cytopathic effect on the kidney. Although an immunological response to viral antigensmay also be theorized as a contributing factor causing renal injury, no histologic evidence thus far has definitively shown this. Lastly, in patients with multi-organ failure and severe Covid-19, the renal injury is likely from a systemic inflammatory response leading to a sepsis-like physiology.

Angiotensin blockade

There remains much concern and debate in the literature regarding the safety of angiotensin blockade in the setting of Covid-19 infections. This has recently been reviewed nicely in great detail and so will only be briefly presented here [10]. It is known that SARS-CoV-2 gains entry into cells through angiotensin converting enzyme 2 (ACE2), which is present both in a soluble form and functions as an enzyme, and as a receptor on alveolar and other epithelial cells including in the heart and kidney. ACE2 is a counterregulatory enzyme that degrades angiotensin II to angiotensin [1-7], thereby attenuating its effects on vasoconstriction, sodium retention, and fibrosis. ACE2 also cleaves angiotensin I to angiotensin [1-9] and participates in the hydrolysis of other peptides. Some animal studies have suggested that Ace inhibitors and ARBs may increase ACE2 expression, increasing viral entry into cells. However, there are insufficient data to support translation of these observations into humans. Moreover, the virus itself downregulates ACE2 expression and thereby may result in local angiotensin II accumulation promoting lung injury and inflammation. Angiotensin blockade, therefore, could in fact be protective by reducing angiotensin II and abrogating its pro-inflammatory and pro-fibrotic effect. Clinical trials are under way to test the safety and efficacy of modulators of this axis and also of recombinant human ACE2, which has already previously beenstudied in clinical trials in patients with ARDS from other causes [11]. Until more data are available, it is suggested that stable patients with Covid-19 not be taken off angiotensin blockade.

As illustrated above, much remains to be learned about this novel virus; it appears too early to know the full extent of the disease manifestations of SARS-CoV-2, the pathogenesis of tissue injury and optimal interventions, both therapeutic and preventative. We are only seeing the tip of the iceberg, and only time and intense research will make us wiser.

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