The SARS CoV-2 Coronavirus-19 Pandemic: A Renal Perspective

Journal CME

By: Sathish George, MD, PhD

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CME Credit Eligibility:
A minimum passing grade of 80% must be achieved. Certificates of credit/completion will be emailed automatically after completion of post-test with a passing grade and course evaluation.

Learning Objectives: Upon completion of this activity, participants should be able to:
1. Cite how the SARS CoV-2 virus replicates within the human body.
2. Identify the impact of SARS CoV-2 on the renal system and patients who become infected.
3. Recognize the impacts of SARS CoV-2 on renal transplant patients.
4. Determine the interaction of Renin-Angiotensin blockers when prescribing to manage hypertension, diabetes, cardiovascular and renal disease, with relation to SARS CoV-2.

Target Audience: This educational activity is intended for physicians.

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Contact Information: For questions, please contact Jackie Owens at evp@acms.net.

At the time of this writing, the SARS CoV-2 pandemic has already resulted in 46 million infections worldwide and 1.2 million deaths. Of these, approximately 10 million cases and 236,000 deaths have occurred in the US, profoundly impacting the lives of many people. It has devastated the economy and severely tested the limits of both medical professionals and the healthcare system. What follows is a general summary of the published data available on the SARS CoV-2 coronavirus as it relates to patients with renal disease.

This virus belongs to the RNA-B-coronavirus group that typically infects the human respiratory, gastrointestinal and central nervous systems. It includes pathogens such as SARS and MERS responsible for severe acute respiratory syndromes. Much like the SARS-CoV virus, SARS CoV-2 exploits its ability to interact with Angiotensin Converting Enzyme -2 (ACE-2) to infect cells. In areas of high ACE-2 expression, such as the oropharynx and gastrointestinal tract, the binding of the SARS CoV-2 viral envelope spike glycoprotein to ACE-2 on the cell surface initiates a clathrin-mediated endocytosis. This process ultimately internalizes the virus and gives it the opportunity to harness cellular transcription mechanisms to replicate itself (Luis D' Marco, Maria et al, Perico, Luca et al).

Patients admitted with a SARS CoV-2 infection can present with hematuria, proteinuria (Farouk, Samira et al) and varying degrees of acute kidney injury (AKI). In a diverse group of studies, AKI was observed in up to 15% of stable hospitalized patients and nearly 50% of those admitted to the ICU, the latter group demonstrating a mortality of almost 35% (Flythe, Jennifer et al). Most of the mechanically-ventilated patients (90%) developed AKI and of these nearly 26% required renal replacement therapy (Hirsch, Jamie et al). In patients who required dialysis the mortality increased to 55% and of those who survived, up to 38% remained dialysis-dependent (Hirsch, Jamie et al, Ng, Jia et al).

Patients with intrinsic renal disease tend to have multiple comorbidities such as diabetes, hypertension, and coronary and peripheral vascular disease that increase their implicit risk profile. Many are also frequently malnourished, sustain a chronically inflamed state and experience uremia-induced changes in Neutrophil, B and T cell function that compromise their innate immunity (Luis D' Marco, Maria et al, Staico, Maria et al). Similar concerns prevail in transplant patients who have to be chronically pharmacologically immunosuppressed. Perhaps related to this issue is the finding that the clinical symptoms of SARS CoV-2 disease in renal patients tend to be more atypical. They often present with less cough and fever and frequently more anorexia, GI distress, fatigue and mental status changes. (Ajaimy, Maria et al, Flythe, Jennifer et al). This situation can often confound the diagnosis as many of these symptoms, especially in end-stage kidney disease (ESKD) patients, can also be attributed to uremia and the sub-optimal delivery of dialysis.
Not surprisingly therefore, chronic kidney disease (Ckd) was found to be 9 times more prevalent in hospitalized patients with SARS CoV-2 related disease and 12 times more prevalent in those requiring ICU admission (Luis D' Marco, Maria et al). ESKD was also associated with a much higher risk of requiring mechanical ventilatory support and the need for ICU level care was associated with mortality rates of almost 50% in both Ckd and ESKD (Flythe, Jennifer et al). Pre-existing renal disease, therefore, appears to be an independent risk factor that confers a poor prognosis in severe SARS CoV-2 related disease.

Renal transplant patients require chronic immunosuppression which increases their inherent infection risk. This occurrence is primarily due to the fact that many of these immunosuppressive agents cause lymphopenia, and in addition, also attenuate the systemic immune response. Fever as a symptom is therefore less commonly seen and patients frequently present without respiratory symptoms or radiological features of a pneumonia (Bassam, G. Abu Jawdeh). In studies of solid organ transplant patients with SARS CoV-2 related disease, the majority of whom were recipients of renal transplants, nearly 80% required hospitalization. Approximately 40 % required ICU level care and of these, 30% required mechanical ventilation and experienced a mortality of 21% (Bassam, G. Abu Jawdeh). Managing immunosuppressive regimens in the face of this disease is therefore complex and also confounded by the prospect that some of these agents may well be capable of temporizing the potentially lethal SARS CoV-2 SIRS mediated cytokine storm. Agents such as Cyclosporine A (CSA) and FK 506 may also have some other unexpected therapeutic benefits as some studies have shown them to be capable of inhibiting the replication of SARS CoV and other coronaviruses in vitro (Bassam, G. Abu Jawdeh) . Although there is as yet no consensus regarding an immunosuppressive regimen in these patients, most transplant programs appear to be systematically withdrawing antimetabolites (mycophenolate) and reducing calcineurin inhibitor (CSA) dosing. In addition, there is also the potential for drug interactions between the various immunosuppressive agents (e.g.: CSA) and experimental SARS CoV-2 therapies (e.g.: Remdesivir) which needs to be followed closely (Adapa, Sreedhar et al).

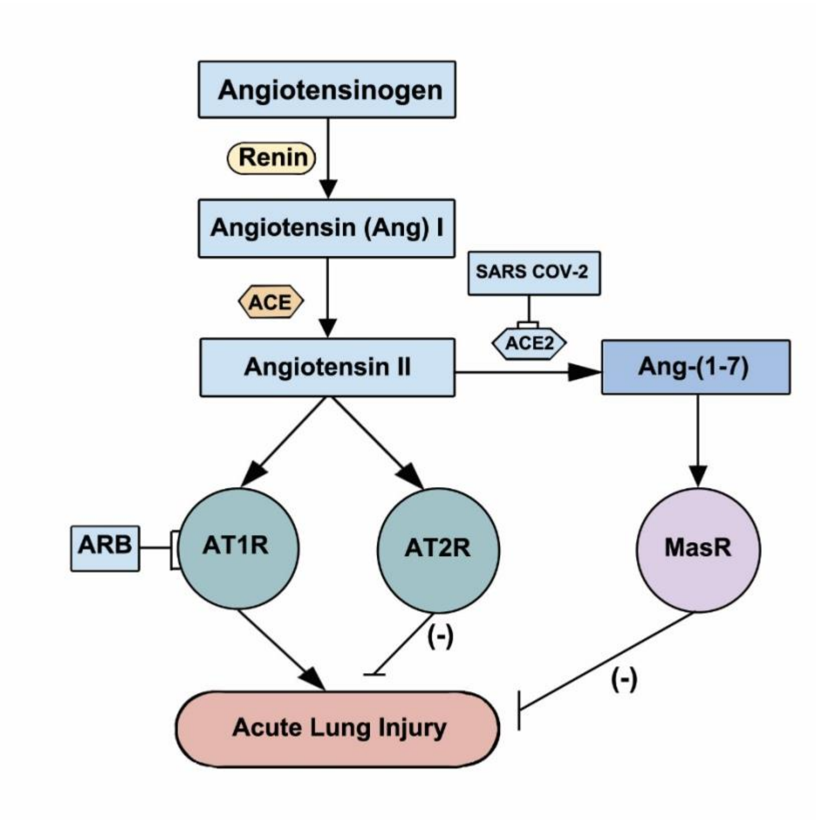
Some investigators have detected SARS CoV-2 in urine. Others have used indirect immunofluorescence, in-situ-hybridization and electron microscopy to demonstrate the presence of the virus in the post-mortem kidney and viral type particles in renal tubular epithelial cells (Farouk, Samira et al, Adapa, Sreedhar et al). These findings together with the hematuria and proteinuria seen with some regularity in this AKI setting (Adapa, Sreedhar et al), have led some to postulate a cytopathic role for the virus in a potential SARS CoV-2 type nephropathy. Interestingly, several case reports of SARS CoV-2 disease associated with collapsing glomerulopathy have now been reported (Batlle, Daniel et al, Santoriello, Dominick et al). However, a recent US post-mortem study of kidney biopsies from SARS CoV-2 patients with AKI, evaluated by similar means, showed no demonstrable presence of the virus in renal tissue (Golmai, Pouneh et al). The causality and significance of this dichotomy in findings is unclear and remains to be clarified. The predominant pathological findings noted in most of the studies correlate with varying degrees of acute tubular necrosis; a plausible finding and likely consequence of systemic infection, sepsis, cytokine upregulation and mitochondrial dysfunction related tubular injury (Golmai, Pouneh et al) .

While vaccine development is being pursued, several therapeutic approaches have been undertaken to treat SARS CoV-2 related disease. Tocilizumab, a monoclonal IL-6 receptor antagonist, has been used in an attempt to mitigate the frequently seen life-threatening cytokine storm. Remdesivir, a RNA dependent RNA-polymerase inhibitor, has been utilized for its potential to interfere with viral replication and, coupled with systemic steroids, to further down-regulate cytokine production, induce lymphopenia and control inflammation (Bassam, G. Abu Jawdeh). Membrane bound ACE-2 is processed by the ADAM 17 protease which liberates its soluble external domain. This moiety retains the capacity to bind SARS CoV-2 and potentially reduce the levels of free virus available to infect cells. Consequently, a clinical trial is underway to evaluate the therapeutic utility of a modified recombinant human ACE-2 administered to SARS CoV-2 patients (Perico, Luca et al). Studies are also ongoing with convalescent plasma, but to date, no definitive therapeutic regimen has been validated.

Drugs that block the Renin-Angiotensin system (e.g.: ARBs) are routinely and successfully used to manage many patients with hypertension, diabetes, cardiovascular and renal disease. These drugs also upregulate the production of ACE-2, the molecule which binds to SARS CoV-2 and facilitates its cellular entry. Continued use of these agents, in patients with SARS-CoV-2 disease, was therefore of some concern owing to their potential to increase the severity of the disease. But studies with other viruses, and particularly Ebola during the outbreak in Sierra Leone, have shown that treatment with ARBs confer a marked survival benefit. Moreover, certain animal models of lung injury and some studies of patients with pneumonia have shown attenuation of the injury in the setting of ARB use (Perico, Luca et al).

Possible explanations for these findings include (see Fig. 1):

Figure 1:



1. Binding of SARS CoV-2 to ACE-2 increases Angiotensin II (Ang II) levels and subsequent lung injury
2. Although binding of ARBs to the AT1 receptor also results in an increase in Ang II, the association of Ang II with ACE-2 induces a conformational change in ACE-2. This situation prevents it from binding the SARS CoV-2 virus and thereby reduces cellular infectivity
3. ARB induced increased Ang II levels result in greater amounts of Ang 1-7 which mitigate the pro-inflammatory effects of Ang II

Given the above data, many medical societies have endorsed the continued rational use of ARBs in SARS CoV-2 related disease as the clinical benefits generally outweigh the risks.

Patients on maintenance hemodialysis are at greater risk for infection owing to their multiple co-morbidities and frequent contact with staff and other patients at the dialysis facility. Their immunizations are therefore closely monitored and kept current and many protocols have been put in place to ensure their continued safety. Mask-wearing by all is strictly enforced and patients and staff are routinely screened for the presence of a fever or any symptoms of illness. All staff wear personal protective equipment per CDC guidelines and dialysis machines are thoroughly disinfected between treatments. Asymptomatic SARS CoV-2 positive patients and those who are recovering are cohorted on specific shifts. They only return to their regular shifts or units after their quarantine period is completed and they test negative for the virus on two separate occasions.

This SARS CoV-2 pandemic has placed an inordinate social, psychological and economic burden on many renal patients. Until a vaccine is forthcoming, it is incumbent upon those of us who care for them to make this difficult transition as safe and tolerable as possible

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CME Post-Test

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CME Post Test Questions (select one answer)

1. SARS CoV-2 exploits its ability to infect cells by interacting with:

A. COX-1 inhibitors
B. Alpha 2 agonists
C. Angiotensin Converting Enzyme - 2
D. Beta Blockers

2. In a diverse group of studies, Acute Kidney Injury (AKI) was observed in up to 15% of stable hospitalized patients and nearly:

A. 20% of those admitted to the ICU
B. 40% of those admitted to the ICU
C. 50% of those admitted to the ICU
D. 60% of those admitted to the ICU

3. Renal patients with SARS CoV-2 disease present with:

A. Less cough and fever
B. More anorexia and GI distress
C. More fatigue and mental status changes
D. All of the above

4. Respiratory symptoms are less frequently seen in renal transplant patients because immunosuppressive agents:

A. Cause Lymphopenia
B. Attenuate the systemic immune response
C. Contribute to antibody production
D. A and B
E. B and C

5. The SARS CoV-2 pandemic has placed an inordinate social, psychological and economic burden on many renal patients.

A. True.

B. False.

6. CKD or ESKD patients with SARS CoV-2 related disease requiring ICU level care experience a mortality of approximately:

A. 30%

B. 40%

C. 50%

D. None of the above

7. While vaccine development is being pursued, several therapeutic approaches have been undertaken to treat SARS CoV-2 related disease including:

A. Tocilizumab.

B. Remdesivir.

C. Systemic steroids.

D. A, B and C

8. Drugs that block the Renin-Angiotensin system are routinely used to manage many patients with:

A. Hypertension.

B. Diabetes.

C. Cardiovascular Disease

D. Renal Disease

E. All of the above.

CME Post-Test

9. Many medical societies have endorsed the continued rational use of ARBs in SARS CoV-2 related disease as the clinical benefits generally outweigh the risks.

A. True.

B. False

10. In studies of solid organ transplant patients with SARS CoV-2 related disease, the majority of whom were recipients of renal transplants:

A. Nearly 80% required hospitalization.

B. Nearly 50% required hospitalization.

C. Nearly 40% required hospitalization.

D. Did not require hospitalization.

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