COVID-19 and the Kidneys: The Renal Impact

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The Kidney and COVID-19: Brief Overview

The ongoing COVID-19 pandemic has caused substantial damage to the health system globally. Though SARS-CoV-2 primarily affects the lungs, it can also affect other organs such as intestines, kidneys, heart and brain. Kidney dysfunctions are also observed in a large proportion of COVID-19 patients.[1] In fact, there is mounting evidence to support that patients with kidney diseases are particularly vulnerable to COVID-19. The vulnerability of patients with diagnosed kidney conditions, with its associated complications, to SARS-CoV-2, is now known. The vulnerability of these patients is attributed to associated comorbidities like diabetes, hypertension and immunosuppressive therapies, among other conditions, that impair their immune system and cause their kidneys to fail.[2]

- It has been observed in a review that a significant proportion of patients hospitalized for COVID-19 have acute kidney injury (AKI), which further deteriorates their prognosis. COVID-19 increases morbidity and mortality among people already diagnosed with kidney disorders and obesity due to multiple organ injury caused by the virus.[2]
- Recently, many studies have examined the impact of COVID-19 on kidney diseases. Scientists found, in a prospective study, that 2% of positive cases had chronic kidney disease (CKD).[3,4]
- Patients with a kidney transplant are also impacted due to their immune-suppression status.[5]
- Incidence of AKI in COVID-19 patients was found to be up to 15% in comparison to the early reports that gave the range of 3–9%.[6,7]
- The incidence of AKI could be up to 25% among critically-ill COVID-19 patients with underlying comorbidities.[7]
- An autopsy study showed virus tropism to the kidney.[8]
- As per the earlier studies, other coronaviruses such as the avian infectious bronchitis virus, are already known to cause severe kidney damage in chicken.[8]

COVID-19 Associated Renal Damage: Mechanism

Covid-19, being a new disease, and the world still being in the claws of the pandemic, makes it difficult to elucidate the mechanisms behind the virus-associated damages, with certainty. Thus, the exact mechanism of SARS-CoV-2 associated renal damage is not fully known. However, the ongoing studies worldwide observe some patterns in this condition. Direct cellular injury due to the virus or sepsis leading to a cytokine storm syndrome is thought to be the possible mechanism connected to the COVID-19 virus. Recently, some studies show that the kidney is one of the target organs for SARS-CoV-2 virus.[2]

Cellular components required for virus entry highly expressed in kidneys

- Studies have shown that cellular components required for virus entry such as angiotensin-converting enzyme 2 (ACE2), cellular transmembrane serine protease 2 (TMPRSS2) and cathepsin L (CTSL) are highly expressed in kidneys.[8]
- Expressions of ACE2 RNA in the small intestine, duodenum and kidneys were found to be much higher (around 100-fold) than in the lungs.[8]
- The co-expression of ACE2 and TMPRSS is reported to be relatively high in the proximal straight tubule cells and podocytes, suggesting favorable conditions for localization of the SARS-CoV-2 in kidneys.[8,9]
- Studies reporting albuminuria and hematuria in COVID-19 patients along with the detection of viral RNA from the urine samples further support the potential tropism of the SARS-CoV-2 to the renal tissues.[1,10]

Cytokine storm of SARS-CoV-2

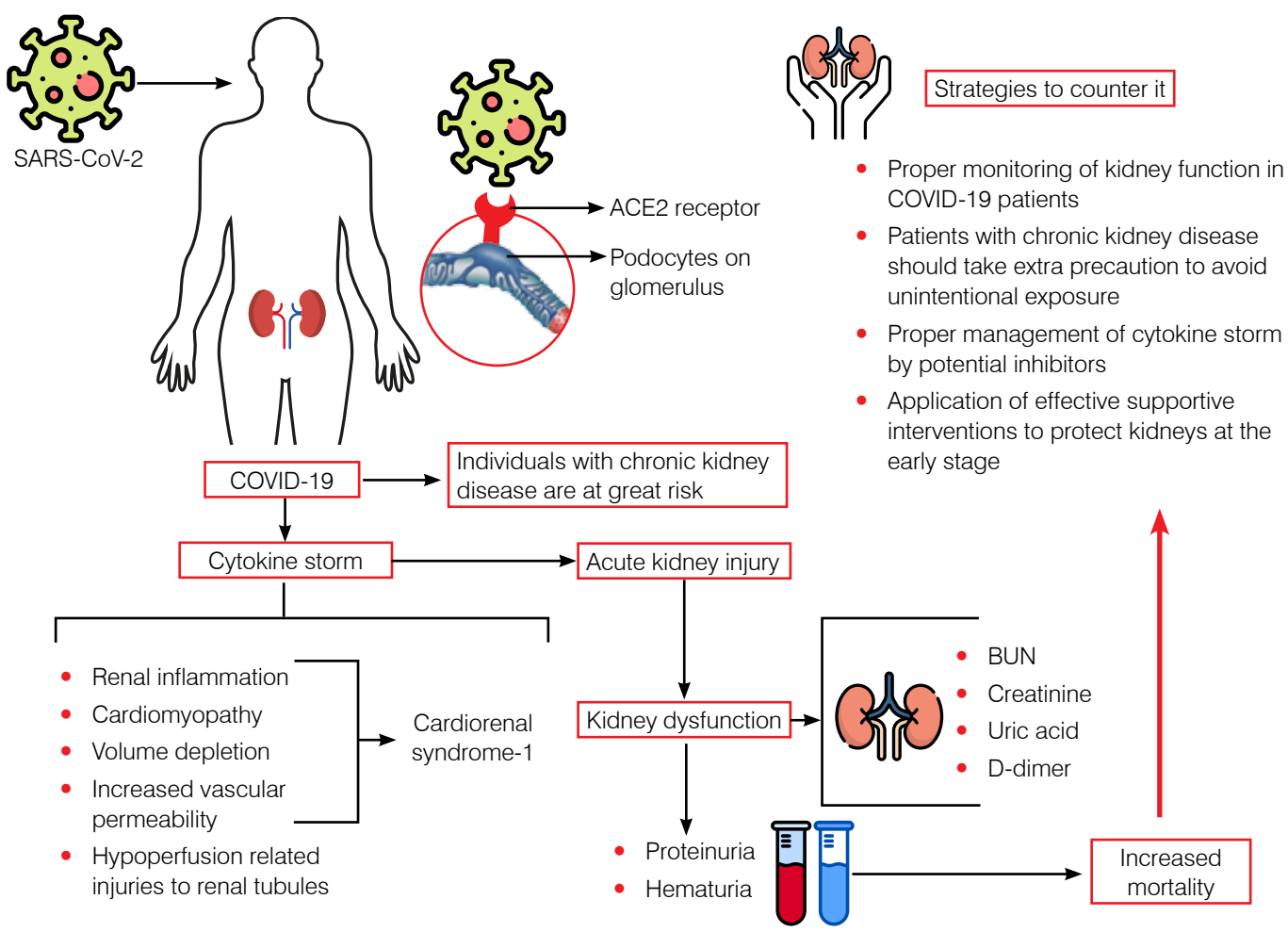
- The cytokine storm associated with the direct cytopathic effect of SARS-CoV-2 is suggested as the probable cause of kidney dysfunction.[8]
- The AKI in response to cytokine storm might occur due to renal inflammation, increased vascular permeability, cardiomyopathy and volume depletion leading to cardiorenal syndrome (Figure 1).[8]
- Injuries of the renal tubules related to the hypoperfusion in response to cytokine storm may also be partly responsible for the kidney injury.[11]
- The computed tomography of the kidneys revealed a reduction in the density suggesting renal inflammation and edema.[1]

COVID-19 in Acute Kidney Injury

Kidney impairment has been found to occur in some COVID-19 patients. More than 50% of the patients admitted in the ICU present with AKI, characterized by elevated serum creatinine, reduced urine output, or both as a result of multiple factors.[12] As per the review done by Dadson and team,[2] the incidence and mortality rates for AKI were 5–15% and 60–90%, respectively. It was also found in the review that about 3.2% of COVID-19 patients developed AKI in the initial stages of infection. Contrary to these findings, one study reported that COVID-19 disease does not result in AKI or aggravate CKD among patients.[2] Nevertheless, the important observations in case of AKI in Covid-19 remain as follows:

- SARS-CoV-2 directly affects the kidney tubules resulting in acute tubular damage and cytotoxicity, and thus, acute renal failure in COVID-19 patients especially among the aged and co-morbid.
- Early renal injury was significantly associated with C-reactive protein (CRP) and neutrophil ratio (NER) indicating that early renal injury was precipitated by severe infection.

Figure 1: Proposed mechanistic approach to COVID-19 associated kidney damage and ways to mitigate it



Abbreviations: SAR S-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; ACE2, angiotensin-converting enzyme 2; BUN, blood urea nitrogen.

Adapted from: Patel SK, Singh R, Rana J, *et al.* The kidney and COVID-19 patients - Important considerations. *Travel Med Infect Dis.* 2020;37:101831.

- Anomalies were found in the estimated glomerular filtration Rate (eGFR) of 66.7%, creatinine clearance (Ccr) of 41.7% and elevated microalbuminuria (UACR) of 41.7% of the patients. These are all important biomarkers that can signify kidney impairment among severe COVID-19 patients and a poor outcome.[2,13]

COVID-19 in Kidney Transplant Patients

Kidney transplant recipients are always prone to opportunistic infections, post-transplant, by viruses. Factors including graft rejection, immunosuppression and tissue injury increase the chance of developing viral infection after kidney transplant. In this scenario, COVID-19 is also not an exception. Findings from various reports are as follows:

- In the presence of the pandemic, a case report found that kidney transplant patients present similar symptoms to what is portrayed in the general population. However, other clinical manifestations, such as hypoxia, chest crepitation, lymphopenia and high CRP were also noted. Besides, very high D dimer, ferritin and troponin levels were also seen among severe COVID-19 cases.[2,5,14]
- In a case report, atypical clinical symptoms such as viral gastroenteritis and oral dehydration were also reported.[15]

COVID-19 in Dialysis Patients

Owing to their immunosuppressed state, kidney patients on dialysis can be considered susceptible to COVID-19 infections.

- These patients are at a high risk of contracting SARS-CoV-2 because of underlying comorbidities, aging and immunosuppression.
- Frequently scheduled visits to hemodialysis centers expose patients to the outside environment, increasing their risk of contracting COVID-19.
- Hemodialysis centers remain high-risk areas for virus transmission to patients, their families and healthcare workers alike.[2,11]

Kidney Patients with COVID-19: Management

The key to successful management of kidney patients with COVID-19 is early detection of renal abnormalities and avoidance of nephrotoxic agents. The needed supportive care should be provided for patients with multiple organ failure.

- It is also important to adhere to the recommended treatment guidelines to manage COVID-19 patients with kidney disorders. It is noteworthy that the drug management targets ACE2 in humans, which serves as a receptor for the virus.
- Administration of glucocorticoids prevents strong immune response and slows the cytokine storm especially among hemodialysis patients.
- The recommended therapy for kidney transplant recipients infected with COVID-19 is a low dose of methylprednisolone-based therapy.[8]

Remdesivir may be used with close monitoring in COVID-19 patients with renal impairment including those with end-stage renal disease (ESRD). It has been found to be well-tolerated in patients with AKI and CKD including those on hemodialysis.[16,17] Early initiation of remdesivir in patients with ESRD and COVID-19 appears to confer clinical benefits in terms of improvement in oxygen requirement, shorter time to recovery and discharge.[17,18] The limited duration (5-10 days) and relatively low dose of 100 mg/day used in COVID-19 infections suggests that benefits of remdesivir outweigh the risk even in patients with eGFR $<30/ml/min/m^2$.[19]

Favipiravir undergoes renal elimination and its plasma levels are 3-5 times higher in patients with eGFR <50 $ml/min/1.73m^2$. However, these levels do not appear to be nephrotoxic and hence can be used without dose modification.[19] Koshi E and colleagues[20] managed a case of ESRD patient with COVID-19 undergoing hemodialysis effectively with favipiravir (3600 mg loading dose followed by 1600 mg administered orally daily in two divided doses, for 2 weeks) and suggest that favipiravir may be an effective option for the treatment of patients with ESRD and COVID-19.

Tocilizumab may be effective in controlling cytokine storm in COVID-19. This was substantiated in a multicenter cohort study[18] of 80 kidney transplant patients with severe COVID-19, wherein treatment with tocilizumab during hospital admission was associated with decrease in CRP levels, and this decrease positively correlated with survival.

A study[21] investigating continuous renal replacement therapy (CRRT) with CytoSorb for patients with life-threatening COVID-19 plus AKI, sepsis, acute respiratory distress syndrome (ARDS) and cytokine release syndrome (CRS) revealed that after 2 ± 1 CRRT sessions with CytoSorb, survivors had decreased SOFA scores, lactate dehydrogenase, ferritin, D-dimers, CRP and interleukin-6; and increased PaO_2/FiO_2 ratios and lymphocyte counts.

Moreover, the Center for Disease Control and Prevention has issued 'Interim Additional Guidance for Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed COVID-19 in Outpatient Hemodialysis Facilities' to reduce the risk in dialysis patients. These guidelines are depicted in Table 1.[22]

Table1: General Measures to Reduce the Risk of COVID-19 in Dialysis Patients

Prevention	Early Recognition	Immediate Referral	Patient Placement	Personal protective equipment (PPE)
• Alcoholic solutions dispensers should be provided in waiting rooms of dialysis facilities. • Accompanying persons and the patient should use hand sanitizer while entering the dialysis facility. • Patients should be advised to use face masks and instructed to cover nose and mouth when coughing or sneezing. Tissues should be discarded in a plastic-lined waste receptacle. • Patients should be advised to wash hands and fistula arm before initiating dialysis and should properly disinfect the cannulation area.	• All symptomatic patients should be identified and screened for novel coronavirus infection. Screening should be done at a single entry to the facility	• Patients having symptoms like progressive breathlessness or signs of adult respiratory distress syndrome should receive an immediate referral to the hospital	• Suspected or confirmed COVID-19 cases should receive hemodialysis in isolation. Separation of at least 6 feet should be maintained between masked symptomatic patients and others	• Dialysis staff should use precautionary measures by using isolation gowns, gloves, masks, and eye protection (shields or goggles). • They should wash their hands with soap and water and use alcoholic based solutions. Surgical masks should be changed every 4–6 h.

Adapted from: Interim Additional Guidance for Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed COVID-19 in Outpatient Hemodialysis Facilities. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis.html. Accessed on 05/04/2021.

Conclusion

Even though we are more than a year into the pandemic, the overall treatment modalities have still not shaped up definitively. Since SARS-CoV-2 is a new virus in humans, further studies are required to design the guidelines for the efficient management of patients with underlying kidney diseases, who are infected with the virus. However, with proactive systematic screening and triaging, close monitoring and prompt management of coexisting infections, the COVID-19 disease burden can be minimized. Patients should be carefully monitored in order to minimize AKI. Even while giving the prescribed drugs, a cautious approach should be followed to avoid worsening the condition of the kidney. The near future should come up with some concrete evidence based modalities to help deal with this virus.

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Uncomplicated Urinary Tract Infections in a 25-year-old woman: A Case Report

Case synopsis

A 25-year-old woman presented with episodes of dysuria, urinary frequency, and urgency. She had previously been diagnosed with remote urinary tract infections (UTIs). Investigations including urine dipstick test results were positive for leukocyte esterase and nitrates. Urine culture was positive for Escherichia coli. On the basis of clinical and laboratory findings, she was diagnosed with uncomplicated UTIs. After being treated with nitorfurantoin 100mg bd for 5 days, her symptoms of uncomplicated UTIs were resolved and improved.

Case Presentation

A 25-year-old woman presented to the department with complaints of dysuria, urinary frequency, urgency, and a one-time episode of hematuria. A careful anamnesis of past medical history reported significant episodes for remote UTIs. She denied fever, chills, nausea, vomiting, or back pain. There was no recent history of surgical procedures or hospitalizations, and she informed that she was not pregnant. Her family history was insignificant for UTIs and renal infections.

Clinical examination

- The patient was well-oriented to time, place and person
- Her vital signs were normal for her age with a heart rate of 92 beats/min and a respiratory rate of 28 breaths/min
- Pallor and icterus were absent
- All findings on the physical examination were normal
- Systemic examination was unremarkable as well.

Laboratory investigations

- CBC: Normal
- Urinalysis: Crystal clear urine
- Dipstick test: Positive
- Urine pH: 7.5 (alkaline in nature)
- Leukocyte esterase and nitrites presented in urine
- WBC/HPF: 6 (abnormal)
- Urine culture: Positive for *E.coli*

Diagnosis

Uncomplicated urinary tract infections

Management

She was prescribed a 5-day course of nitrofurantoin 100 mg twice per day. She was also prescribed Flavoxate 200 mg thrice daily, as she was having dysuria and other lower urinary tract symptoms. Along with this she was asked to keep herself hydrated by drinking plenty of water. There was no organism detected when she underwent urine examination (Routine microscopy and culture sensitivity). She experienced relief from her symptoms of urinary tract infection.

Discussion

Urinary tract infection (UTI) is commonly encountered by clinicians worldwide that, traditionally, may be classified depending upon the site of infection, as upper UTI (infection of the kidney and ureter) or lower UTI (infection of the urinary bladder and urethra); depending upon the presence or absence of symptoms, as symptomatic or asymptomatic UTI.[1,2]

Its etiology comprises a variety of pathogens among which the most common are *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis* and *Staphylococcus saprophyticus*. Owing to a high recurrence rate and an increased antimicrobial resistance, it is known to impose a significant economic burden.[3] A higher incidence of UTIs is seen in women than in men, at a ratio of 8:1.[4]

It is a highly prevalent condition affecting 150 million people annually. Although antimicrobial therapy is found to be effective in treating most of the cases, recurrence is commonly associated with UTIs. The common clinical features of a UTI include dysuria, urinary frequency, urgency, suprapubic pain, possible hematuria, cloudy urine and a urinary odor.[4]

Nitrofurantoin: An effective antimicrobial for UTIs in current era of resistance

UTIs are one of the most common reasons for antibiotics prescription. However, inadvertent use of antibiotics has led to an emergence of resistant strains, which can withstand these antibiotics and continue to thrive and multiply in the adverse environments engendered by them.[1,5] This makes it pertinent that antibiotic resistance and susceptibility patterns of the most frequent uropathogens implicated in UTI are continuously evaluated to help tailor appropriate empiric antimicrobial regimen.[6]

Nitrofurantoin seems very close to this need as it was found to exhibit very low resistance rates against urinary isolates of *E. coli* in UTI patients, compared to other commonly used antibiotics.[7]

In some European countries, 100 mg nitrofurantoin twice daily for five days, has been considered among first line empirical antibiotic treatment for the treatment of uncomplicated UTI for both lower and upper urinary tract acute symptomatic infections.[8] In a study by Kranjčec *et al*[9] that evaluated efficacy of different prophylactic regimens versus no prophylaxis in urinary tract infections. It was revealed that the rate of recurrent infections was lower in the nitrofurantoin prophylaxis group in comparison to no prophylaxis group and nitrofurantoin was well tolerated by the patients.

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