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Novel therapeutic approaches for COVID-19 in chronic kidney disease and transplant

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Purpose of review
Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is the novel virus responsible for the current worldwide pandemic. The scientific and healthcare communities have made every effort to discover and implement treatment options at a historic pace. Patients with kidney disease are uniquely vulnerable to an infectious pandemic because of their need to be in frequent contact with the healthcare system for life-sustaining renal replacement therapy whether it be by dialysis or transplant.

Recent findings
The use of targeted viral therapies, extracorporeal therapies, immunosuppressive therapy and public health interventions are important in the management of patients with COVID-19 but require special consideration in patients with kidney disease because of the complexity of their condition.

Summary
Here, we discuss some of the major efforts made to prevent spread and emerging treatment options for this virus, as they pertain to patients with kidney disease.

Keywords
antiviral therapy, COVID-19, end-stage kidney disease, extracorporeal therapies, kidney transplantation, remdesivir, SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2

INTRODUCTION

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is a novel virus discovered in December 2019 in Wuhan, China, where it was noted to be responsible for an increasing number of individuals with atypical pneumonia [1▪]. This presumed zoonotic infection was linked to a local live animal market, and despite local measures to halt the spread of infection, the number of cases continued to rise. The spread of Corona Virus Disease 2019 (COVID-19), the name now used to refer to the disease caused by SARS-COV-2, was closely monitored by the WHO. The WHO escalated the disease from a public health emergency of international concern to the level of pandemic in early March 2020. As of late July 2020, there have been over 16 million worldwide cases of confirmed COVID-19, and over 650,000 deaths attributed to this viral infection [2]. As a result, communities and healthcare resources around the world have been strained to their limits. There has been an enormous effort by the scientific community, unparalleled in modern history, to better understand the nature and pathophysiology of this disease. The hope is that these advances will expedite safe and effective therapeutic interventions to the bedside.

As we continue to learn more about COVID-19, we have developed an understanding that immunosuppressed patients, like those who are dialysis dependent and those who have received a solid

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KEY POINTS

- Patients with kidney disease are uniquely vulnerable to an infectious pandemic because of their need to be in frequent contact with the healthcare system for life-sustaining renal replacement therapy whether it be by dialysis or transplant.
- Remdesivir not currently used in the treatment of patients with ESRD and COVID-19 is likely well tolerated and needs further evaluation given that toxic accumulation of cyclodextrin can be mitigated by removal with dialysis.
- Extracorporeal therapies currently underutilized may not only play a greater role in the management of critically ill patients with hyperinflammation but also novel hemoperfusion filters may have a direct role in viral neutralization.
- Improving general nutrition of patients with kidney disease can improve gut microbiome an essential component of immune protection.

organ transplant, are at an increased risk for complications following a COVID-19 infection. The risk factors for severe COVID-19 related illness, such as diabetes mellitus and hypertension, are also concentrated in patients with chronic kidney disease (CKD). As a result, nephrologists around the world are challenged to address the complications of COVID-19 in an already fragile population [3]. We will review new approaches towards the treatment of CKD in the midst of this pandemic, focusing on interventions that limit viral spread, viral-directed therapies, strategies to manage the critically ill patient and the potential means of improving the general health and immunity. Our knowledge of this coronavirus is rapidly evolving, and the understanding of the therapeutic interventions discussed here is likely to rapidly improve and change as we learn more about this new disease.

LIMITING SPREAD

From the beginning, public health interventions have been touted as our greatest weapon to limit the spread of this new disease. Despite this, a variety of social and economic elements resulted in variable implementation of recommendations around the world. Countries and local communities struggled to determine their individual risk for outbreak, as well as balancing the effect that public health interventions would have on the economic infrastructure needed to sustain the communities through and beyond a pandemic. In the USA, initial efforts to reduce viral spread with 'stay at home orders', and 'the practice of 'social distancing', in many high-risk communities seemed effective based on the initial plateauing of cases. However, we are now facing a resurgence of infections following loosened restrictions and early reopenings.

There is a growing body of evidence to support that the primary mode of viral transmission in the community is from person-to-person, and that personal protective equipment can limit the spread of infection [4,5]. Despite this our knowledge of the virus is incomplete, research continues to enhance our understanding on a regular basis. It is apparent that those at greatest risk for infection are those in close contacts with already infected individuals. This is of particular importance for patients with CKD who by the nature of their disease are often clustered together for essential treatments. Whether this be in the lobby of clinics, or in dialysis centres for more extended periods to receive the in-centre treatments that the majority of US patients requiring renal replacement therapy receive. With viral spread likely starting days before the onset of symptoms and extending well into the symptomatic period, providers have been challenged to modify and redefine the traditional treatment space for patients with kidney disease [6].

There have been multiple interventions in these treatment spaces aimed at reducing the risk of transmission. Although not altogether new to healthcare, the rapid implementation of Telehealth visits during the COVID-19 pandemic has changed routine delivery of care. Patients with CKD continue to require regular contact with their providers for symptom and disease management given the complexity of their illness; telehealth has allowed patients to do this from the comfort of their home, limiting contact and exposure for essential blood draws and procedures. In this fashion, they will continue to receive essential care that prevents the deterioration in their health from chronic conditions and reduce the need for hospitalization in the midst of a pandemic. A complete withdrawal from healthcare would otherwise likely result in increased morbidity and mortality, due to rapidly escalating complications of untreated CKD and increase the number of otherwise preventable hospitalizations [7].

Traditional in-centre dialysis poses inherent challenges when the primary means of preventing disease is avoiding contact. The traditional model cohorts a large number of at-risk individuals in a limited space to receive life sustaining therapy. There has recently been a major push to increase the number of patients receiving home therapies with the obvious benefit of reducing the need for direct in-person contact and to better allow patients

to quarantine if infected or exposed. However, not every patient receiving in-centre therapy is able to transition to his or her home for a multitude of reasons, and initiating that process in the midst of a pandemic is logistically challenging. As a result, regular screening of patients has become the standard of care at dialysis centres across the nation. A variety of isolation techniques have been implemented separating noninfected patients, those under investigation for infection and those who have confirmed infection from one another. Grouping patients by risk of infection has become standard with terminal cleaning occurring between treatment groups [8].

Kidney transplantation remains the optimal treatment for most patients with end-stage renal disease, and transplant centres face unique challenges in continuing their mission in the face of an infectious pandemic. They must balance limited healthcare resources, limited access to critical supplies and increased risk of infection to an immunocompromised host, as well as the risk of death from COVID-19 against the risk of morbidity and mortality associated with delay of transplantation and continuation of dialysis. Maximizing efforts to reduce delayed graft function, anticipating earlier hospital discharges with preestablished adequate home support, in combination with frequent telehealth communication has allowed some programs to continue to operate, albeit with a staged reduction in transplant volume based on health system capacity and degree of viral spread in each centre's local community [7].

TARGETED VIRAL THERAPIES

Remdesivir is an antiviral agent initially developed through a collaboration between Giliead Science, the CDC, and the US Army Medical Research Institute as a therapeutic intervention against RNA viruses with pandemic potential. As a result of the 2014 Ebola virus (EBOV) outbreak, researchers prioritized efforts to identify an agent with particular efficacy against EBOV. Since that time, multiple groups have shown the in-vitro and in-vivo efficacy of remdesivir against several viruses. In the fight against Ebola, it was found to be inferior to antibody-based therapeutics limiting its role. However, from these studies, valuable patient safety data were collected, and it is generally a well tolerated agent. Intracellularly, it is metabolized to an analogue of adenosine triphosphate, which can inhibit viral RNA polymerases with previously known activity against other coronaviruses. Early on in the current pandemic in-vitro studies of remdesivir demonstrated activity against SARS-COV-2 prompting Gilead Science and researchers' interest to investigate its potential as a treatment for COVID-19 [9].

Early reports from clinical trials in the treatment of COVID-19 provide data that continue to support the notion of the potential therapeutic benefit of Remdesivir [10]. Preliminary reports from a multinational trial showed improved recovery time in patients hospitalized with COVID-19 pneumonia that received Remdesevir [11▪]. Ongoing clinical trials will further delineate its true impact on mortality on a wider range of patients afflicted with COVID-19. Of particular concern are the pharmacokinetics of remdesivir in patients with severe renal impairment. This stems from its limited water solubility, requiring preparation with vehicle sulfabutylether-ß-cyclodextrin (SBECD) for intravenous delivery. Although cyclodextrin has the potential to accumulate in renal impairment, there are data from its use in other intravenous agents, particularly voriconazole [12]. These data highlight its dialyzability and safety in short courses. Given the morbidity associated with COVID-19 infections, particularly in patients with severe AKI requiring dialysis and ESRD, the potential benefit from short courses wherein dialysis is likely to remove the accumulation of cyclodextrin before toxic accumulation outweighs the risks of its use [13▪]. Unfortunately, exclusion criteria for the vast majority of clinical studies following the FDA emergency use authorization has prevented the majority of patients with severe renal impairment from receiving this potentially beneficial therapy.

Passive antibody-based immunity is a historical therapy repurposed with the notion that convalescent plasma obtained from individuals who have recovered from infection will have an abundance of SARS-CoV-2 directed antibodies, which when transfused to an afflicted individual will reduce the clinical severity and burden of the disease. Historical studies have established the safety of convalescent plasma use, and preliminary reports support its role in the treatment of COVID-19 [14]. Hyperimmunoglobulin is being manufactured from pooled plasma donors who have recovered from COVID-19, and once available should improve access to passive antibody infusion availability [15]. Convalescent plasma and hyperimmunoglobulin are viable treatment options in the midst of this pandemic when a large number of recovered individuals are available to donate; however, this is unlikely to be a sustainable long-term therapeutic option. Donating plasma can provide a psychological benefit, motivating those who have recovered to help those actively infected and may help to maintain our short-term supply [16]. The risks of convalescent plasma are the same as that of any plasma transfusion. Its use in

patients awaiting kidney transplantation may result in increasing sensitization, and as a result may not benefit individuals with renal impairment and mild COVID-19.

There is ongoing research to develop mAbs for the prevention and treatment of COVID-19. This may further improve accessibility to passive immunity, and would likely remain available after the pandemic, despite decreasing available donor pools [17]. Selecting and duplicating a specific antibody, or groups of specific antibodies, with high neutralizing ability has a greater likelihood of clinical benefit and has been shown to be effective in the treatment of another deadly virus, Ebola [18]. Several clinical trials of monoclonal antibodies against SARS-CoV-2 are preparing to enrol patients at this time.

Developing a vaccine for SARS-CoV-2 has received enormous media attention, and the ongoing efforts to develop a vaccine have become the holy grail of the scientific community because of the potential to rapidly induce heard immunity and halt the unopposed spread of infection. Unlike previous vaccine development projects that have required decades to develop, the anticipated timeline for vaccine availability has been touted to be less than 2 years. With enormous effort focused on vaccine development, it is remarkable that the number of varied approaches from scientists around the world, using their personal experiences from other applications, particularly immunotherapy, to expedite a new and hopefully effective vaccine to market [19]. The details of many of these vaccine projects are not publicly available, but many projects have transitioned from exploratory to preclinical investigations and phase 1 trials [20]. The vast majority of vaccine development projects are not using live-attenuated virus technology, making it more likely that they will be a safe option for immunocompromised patients, particularly those who have previously received a solid organ transplant.

TREATMENT OF THE CRITICALLY ILL PATIENT

One of the defining characteristics of severe Illness in COVID-19 is a hyperinflammatory syndrome that typically accompanies acute respiratory distress syndrome (ARDS) in critically ill patients. The clinical presentation and cytokine profile in these patients have led to the use of immunosuppression in an effort to blunt the immunoinflammatory response that accompanies severe illness. Toculizumab, a mAb that blocks the IL-6 receptor and has been used for the treatment of cytokine release syndrome, which is a hyperinflammatory state associated with immunotherapy that is clinically similar to what has been seen in severe COVID-19 infection [21,22]. Early clinical investigations have shown mixed results, potentially confounded by the severity of illness, in these largely observational studies and further data from randomized clinical trials will be useful in establishing the actual efficacy [23,24]. Similarly, the role of complement activation in ARDS has prompted investigation as to whether C5 inhibitors may reduce cytokine levels and as a result reduce lung inflammation and injury [25]. Enrolment in clinical trials is ongoing as a result of favourable case reports with the use of eculizumab [26].

Extracorporeal therapies have been proposed as a means of removing cytokines from critically ill patients. Although not typically available in the United States, hemoperfusion, haemodialysis with high cut-off dialysis membranes and CKRT-utilizing filters with adsorptive properties have been used elsewhere for this purpose [27]. Proinflammatory cytokines have an association with lung injury and ARDS. There is also an association between lung and kidney injury with cytokine overproduction and hyperinflammation. The exact pathophysiologic mechanism of this relationship has yet to be fully characterized; however, available evidence suggests that a close relationship between organ injuries exists, and that the effect on the kidney likely potentiates lung injury and vice versa [28]. The prevalence of AKI requiring kidney replacement therapy accompanying ARDS requiring mechanical ventilation in patients with severe COVID-19 seen in the United States and Europe gives credence to the notion that cytokine removal may reduce or prevent organ damage in severe illness [29]. Cytosorb, an adsorbent cartridge that has now been granted emergency use authorization by the FDA, is reintroducing sorbent technology to the United States market after early reports suggesting benefit from Italy, China and Germany [30▪]. Another hemoperfusion filter Seraph 100 Microbind Affinity Blood Filter has also recently received emergency use authorization for treatment of COVID-19. Unlike other sorbent devices, Seraph 100 cannot only remove cytokines, but because its media composition utilizing heparan sulfate, it can additionally bind and remove bacteria, viruses and endotoxin from the blood [31]. The Department of Defense is providing funding and carrying out a USA-based randomized controlled trial after encouraging preliminary reports from its use in critically ill patients with COVID-19 [32▪]. These clinical trials will be essential in establishing the role of adsorptive technology, not only in COVID-19, but perhaps in other septic illnesses and

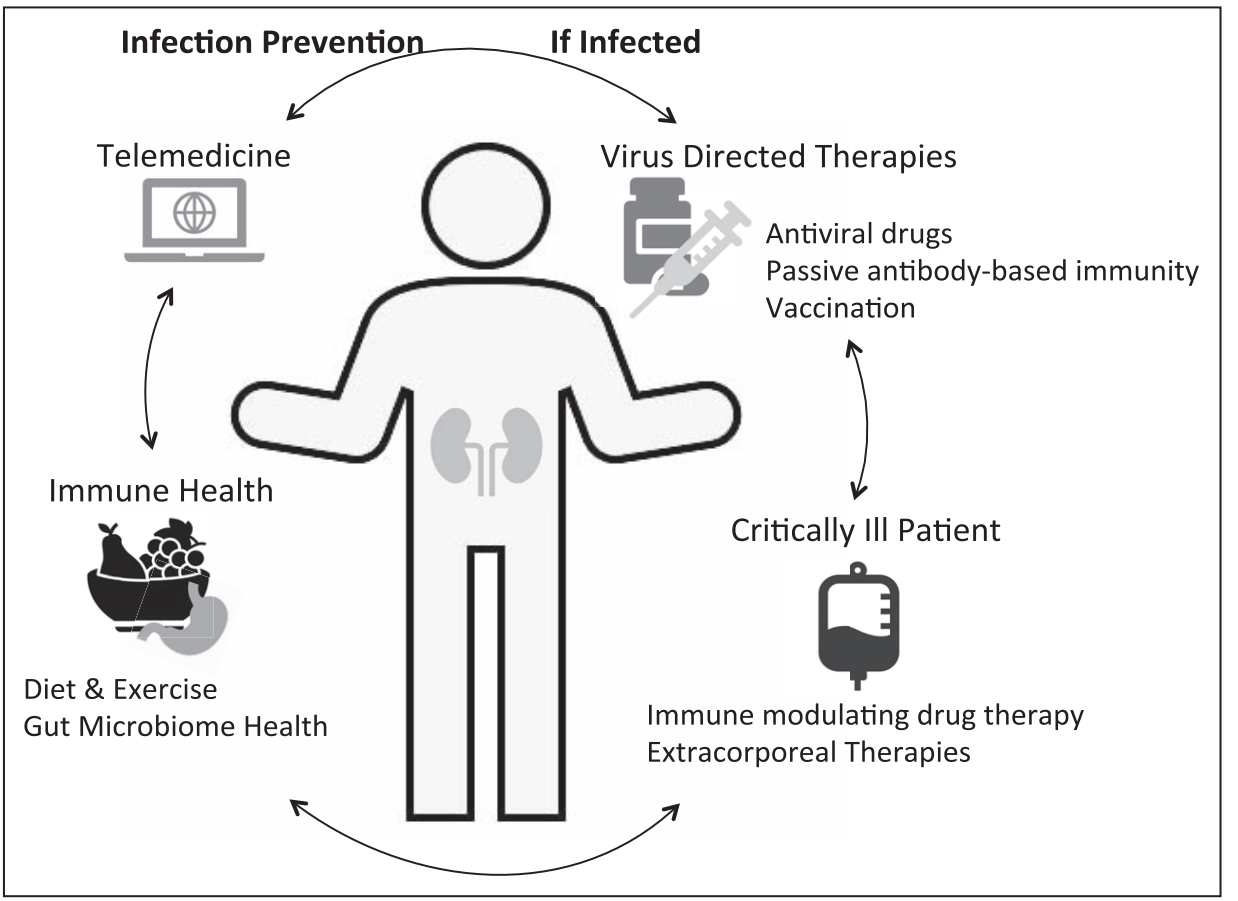

FIGURE 1. Multifaceted approach to care of patients with renal disease during COVID-19 pandemic.

hyperinflammatory conditions. They may even play a role in the treatment of currently problematic multidrug resistant organisms.

IMPROVING IMMUNITY AND GENERAL HEALTH

The effects of SARS-CoV-2 infection are not limited to respiratory disease and multiorgan failure in the critically ill. In fact, there is growing body of literature recognizing the wide systemic effects of COVID-19 in other organ systems, including dermatologic, neurologic and psychiatric illness amongst others [33,34]. Even the mechanisms of kidney injury and potential long-term kidney manifestations are unknown; renal disease reviewed from postmortem and living specimens has varied and it is not yet clear to what extent, if any, the direct viral infection has on kidney function, or whether the majority of injury is a result of amplified immune response and related cytokine effect [35,36]. Given the widespread clinical manifestations and varying degrees of illness, it is not a large surprise the worldwide mortality of COVID-19 disease varies greatly by afflicted region. Although there may be many reasons, including issues related to access to care and differing virulent strains afflicting different geographic regions. The overall health of a population, and poor nutrition of some groups, may increase the risk of severe disease. Malnutrition and poor dietary habits are common across the United States, and we have struggled with an obesity epidemic for many years. The obese patient is at a greater risk of baseline respiratory dysfunction, and typically have comorbid conditions that further increase their risk of severe manifestations and critical illness with COVID-19 [37]. The gut microbiome is an essential component of immune protection and clearly affected by malnutrition. In fact, patients with CKD are well known to have alterations in gut microbiome that impair the intestinal epithelial barrier and contribute to the systemic inflammation seen in this population [38]. The abundance of ACE2 receptors on intestinal epithelial cells, altered gut microbiome and increased inflammation may be part of the reason patients with CKD are at risk for severe illness. Diagnostic and therapeutic interventions utilizing

nanotechnologies have been proposed, providing a direct mechanism to alter the affected gut microbiome [39]. This pandemic again brings additional evidence to support strategies dedicated to improving the dietary health of our population as a means of not only reducing comorbid conditions and improving general health, but also improving overall immune health and resilience against future infections.

CONCLUSION

As the pandemic evolves so will our understanding of therapeutic interventions, which have the potential to change outcomes, particularly in patients with kidney disease who are in regular contact with the healthcare community given the complexity of their illness (Fig. 1). A vaccine has the greatest potential to limit spread of illness, but the rapid development of other novel therapies may help us combat this disease in the interim.

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Conflicts of interest

There are no conflicts of interest.

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