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COVID and the Kidney: An Update

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Summary
Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has led to a global pandemic that continues to be responsible for ongoing health issues for people worldwide. Immunocompromised individuals such as kidney transplant recipients and dialysis patients have been and continue to be among the most affected, with poorer outcomes after infection, impaired response to COVID-19 vaccines, and protracted infection. The pandemic also has had a significant impact on patients with underlying chronic kidney disease (CKD), with CKD increasing susceptibility to COVID-19, risk of hospital admission, and mortality. COVID-19 also has been shown to lead to acute kidney injury (AKI) through both direct and indirect mechanisms. The incidence of COVID-19 AKI has been decreasing as the pandemic has evolved, but continues to be associated with adverse patient outcomes correlating with the severity of AKI. There is also increasing evidence examining the longer-term effect of COVID-19 on the kidney demonstrating continued decline in kidney function several months after infection. This review summarizes the current evidence examining the impact of COVID-19 on the kidney, covering both the impact on patients with CKD, including patients receiving kidney replacement therapy, in addition to discussing COVID-19 AKI.

Keywords: Acute kidney injury, COVID-19, chronic kidney disease, dialysis, transplant, vaccination

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is thought to have originated by zoonosis in Wuhan, China, in December 2019, leading to a global pandemic,[1] which continues to have ongoing health consequences for people worldwide. As of August 13, 2023, there has been more than 769 million confirmed cases of COVID-19 and more than 6.9 million deaths globally.[2] Among the worst affected have been individuals with comorbidities such as diabetes, hypertension, and chronic kidney disease (CKD), and immunocompromised individuals such as kidney transplant recipients. The SARS-CoV-2 virus leading to the COVID-19 pandemic has been shown to impact the kidney in several different ways. This ranges from mild proteinuria to the need for kidney replacement therapy (KRT). The pandemic also has had a significant impact on patients with underlying CKD, with studies suggesting that CKD increases susceptibility to COVID-19, is associated with risk of hospital admission, and increased severity of disease and adverse outcomes. Furthermore, the COVID-19 pandemic has had a devastating effect on the dialysis and transplant community; not only have many people died from the infection itself, but also from the increased poverty and strain on the health system that it caused.[3] Moreover, with the roll out of vaccines and emergence of viral variants, understanding and protecting against COVID-19 remains a priority for transplant and dialysis recipients. As the pandemic has evolved, there is increasing evidence examining the long-term effects of COVID-19 on the kidneys.

In this review we first discuss COVID-19 AKI, covering the incidence, pathophysiology, risk factors, and outcomes. Second, we examine the impact of COVID-19 on individuals with CKD, and, third, the impact of the pandemic on patients receiving KRT (dialysis and transplant), reviewing the latest updates on preventative and treatment strategies. Finally, we discuss the emerging evidence examining the longer-term effects on the kidneys.

COVID-19 DISEASE

Of patients diagnosed with symptomatic COVID-19, the most frequent symptoms are fever, cough, tiredness, and loss of taste or smell,[4] although symptoms vary between viral variants and affected populations. Severe forms of

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the disease occur in a small proportion of individuals, most commonly manifesting as acute respiratory distress syndrome and respiratory failure.[5] Severe disease results from damage to the respiratory system caused by a state of hyperinflammation attributed to a cytokine storm, and is associated with increased age and comorbidities.[6,7] The SARS-CoV-2 virus gains entry to affected cells via the viral spike protein binding to the Angiotensin-converting enzyme-2 (ACE-2) receptor. This receptor ligand interaction is critical because vaccine-induced antibody directed against the viral spike protein (the immunogen in the vaccines) is an essential component of immunity against both infection and disease.[8] Although often overlooked in the early days of the pandemic, the role of the cellular immune system, and particularly the $CD8^+$ T-cell response, is important for clearance of virally infected cells to prevent severe and protracted illness. The contribution of T-cell immunity to clinical outcomes is notoriously difficult to measure because it is masked by an effective neutralizing antibody response. However, CD8 T cells are associated with reduced mortality in patient populations lacking the neutralizing antibody,[9] and are associated with mild disease in nonimmunocompromised individuals.[10-13] Individuals with kidney failure and especially immunosuppressed kidney transplant recipients (KTRs) are at risk of developing a poor $CD8^+$ T-cell response.

COVID-19 AKI EPIDEMIOLOGY

At the start of the pandemic, initial reports from China suggested that AKI was uncommon in patients hospitalized with COVID-19. However, subsequent studies primarily from the United States and Europe have shown rates as high as 40%, with many patients requiring KRT. A systematic review including 49,048 patients hospitalized with COVID-19 AKI showed that there was significant geographic variation, with a pooled incidence of 5.5% in Asia compared with 28.6% in studies from the United States and Europe.[14]

The reasons behind these observed differences may be owing to differing thresholds for admission for COVID-19, AKI definition, and, possibly, differences in demographics of the populations examined. As the pandemic has evolved, studies have found that the incidence of both AKI and the need for KRT has decreased.[15-17] Charytan et al[17] showed a reduction in AKI incidence in a study of 4,732 admissions for COVID-19 between March 2, 2020, and August 25, 2020, in New York City. They found a marked reduction in AKI incidence over time, with a rate that was one-third lower during the last 7 weeks compared with the first half of the surge. Data from 5,498 patients also from New York City between March 1, 2020, and April 30, 2021, showed that AKI incidence in patients hospitalized for COVID-19 had decreased.[15] A prospective multicenter study of 85,687 patients admitted to hospitals in the United Kingdom with COVID-19 between January 2020 and December 2020 reported that rates of AKI reached a peak in April 2020 at 33.8%, but then decreased.[18]

There are several reasons thought to be contributing to this reduction. This includes improved management with more liberal fluid management. At the outset of the pandemic, common practice was to restrict fluid administration and administer diuretics, which further exacerbated AKI. Improved recognition as well as the advent of effective treatment options for severe COVID-19 in addition to vaccination programs and changes in variants all are likely to have led to this observed reduction.

PATHOPHYSIOLOGY OF COVID-19 AKI

COVID-19 AKI is usually multifactorial. In keeping with this, the most common pathologic feature present on kidney biopsy and post-mortem examination is acute tubular necrosis.[19,20] In non−critically ill patients with proteinuria, collapsing glomerulopathy has been described. This is associated with high-risk Apolipoprotein L1 (APOL1) genotypes, mainly in Black men.[21]

The pathophysiology of COVID-19 AKI is complex, with both direct effects on the kidney in addition to indirect effects (Fig. 1). The impact of direct renal tropism is unclear, with viral particles seen in some studies but not others. This may be related to the timing of kidney biopsies. Clinical studies showing an association between viral load and severity further support this theory.

Other direct effects of the virus include endothelial injury and activation of coagulation pathways, complement activation, local inflammation, and thrombotic microangiopathy.[22] Indirect mechanisms can be related to the systemic effects of infection including sepsis, hypoxia, hypovolemia, organ cross talk, and hemodynamic instability. Detailed discussion of these pathologic mechanisms is out of the scope of this review.

RISK FACTORS FOR AKI IN COVID-19

Risk factors for COVID-19 AKI are not dissimilar to AKI in any setting and are shown in Figure 2. Patient-related risk factors include older age, male sex, Black race, high body mass index, and comorbidities such as diabetes mellitus, hypertension, congestive heart failure, and underlying CKD. Genetic factors also have been shown to play a role. APOL1 genotyping studies have shown that high-risk APOL1 alleles are associated with higher odds of AKI, need for KRT, and death in patients with COVID-19. This is thought to be due to an increased inflammatory response to COVID-19 in carriers leading to kidney injury. A recent systematic review of 153,600 patients with COVID-19 from 39 studies showed that age; male sex; obesity; Black race; invasive ventilation; and the use of diuretics, steroids, and vasopressors; in addition to comorbidities such as hypertension, congestive heart failure, CKD, acute respiratory

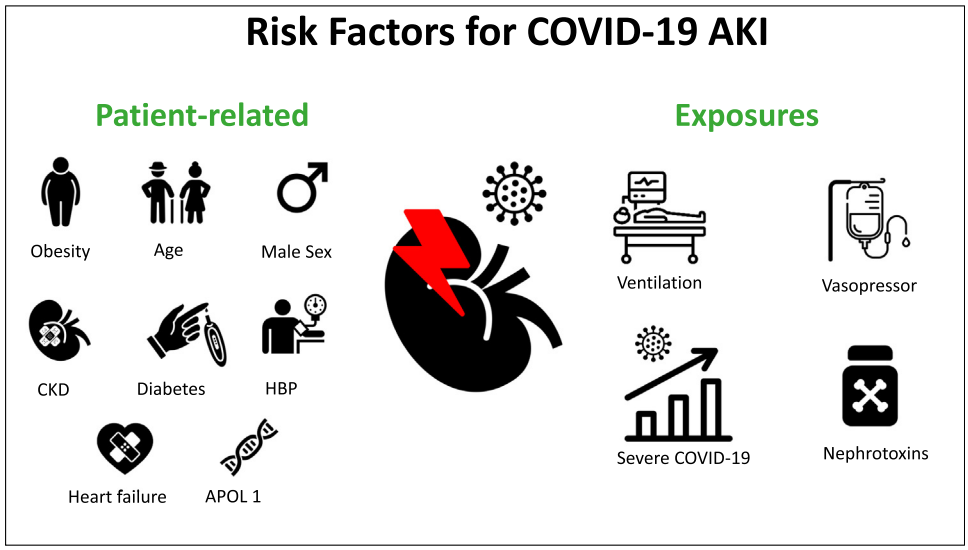

Figure 1. Pathogenesis of coronavirus disease-2019 (COVID-19)−associated acute kidney injury (AKI) showing both the direct viral effects of COVID-19 on the kidney and the nonviral pathogenic mechanisms contributing to AKI, including those related to critical care. Abbreviations: APOL1, apolipoprotein L1; CKD, chronic kidney disease; HBP, _hypertension.

distress syndrome, and diabetes, were significant risk factors for COVID-19−associated AKI.[23]

Risk factors for AKI evident at admission are related mainly to the severity of COVID-19 with hypoxia, increased inflammatory markers, and evidence of organ damage associated with increased risk. In common with all AKI, risk factors for developing COVID-19 AKI during hospitalization include a requirement for mechanical ventilation, vasopressor use, and use of nephrotoxic medication.

OUTCOMES AFTER COVID-19 AKI

Several large studies have shown that COVID-19 AKI is associated with increased mortality, with risk increasing as the severity of COVID-19 increases.[24,25] A prospective multicenter cohort study of patients admitted to 254 UK hospitals showed that the risk of 28-day mortality increased with increasing severity of AKI: stage 1 adjusted odds ratio (aOR) of 1.58 95% CI (1.49−1.67), stage 2 aOR of 2.41 95% CI (2.20−2.64), stage 3 aOR of 3.50 95% CI (3.14−3.91), and KRT aOR of 3.06 95% CI (2.75 −3.39).[18] It remains unclear whether AKI plays a causative role in the increased mortality rate or whether it is a prognostic factor.

It is well established that AKI can lead to CKD. However, there are few studies examining the long-term effects of COVID-19 on kidney function. Many of the direct and indirect pathologic processes described earlier may persist in the longer term and may predispose the kidneys to recurrent episodes of AKI. The majority of studies are limited to the short term, with limited data examining kidney function more than 1 year after AKI. A multicenter observational cohort study of 12,891 hospitalized patients with COVID-19 found that patients with COVID-19 −associated AKI had significant and persistent increases of baseline serum creatinine concentrations of 125% or more at 180 days (risk ratio, 1.49; 95% confidence interval [CI], 1.32-1.67) and 365 days (risk ratio, 1.54; 95% CI, 1.21-1.96) compared with COVID-19 patients with no AKI.[25] In a multicenter cohort of 4,221 critically ill patients with COVID-19 admitted to intensive care units at 68 US hospitals, Hsu et al[26] showed that greater AKI severity was associated with a higher in-hospital mortality rate and, among survivors, worse kidney function at

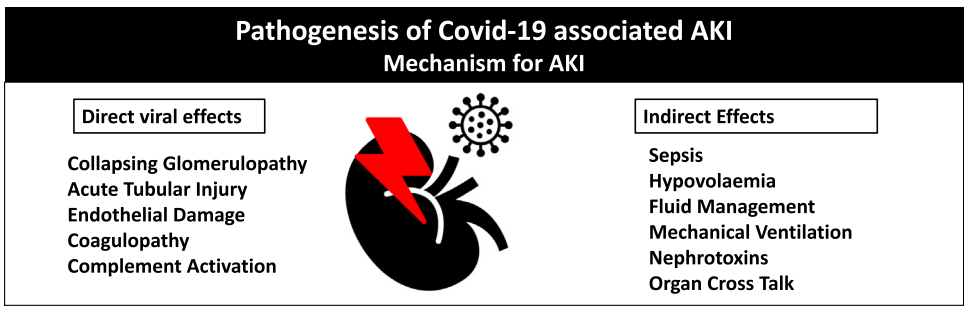

Figure 2. Risk factors for developing coronavirus disease-2019 (COVID-19) acute kidney injury (AKI) separated by patient-related factors and exposures.

discharge. They also found that almost two thirds of patients who had AKI and were treated with KRT died. Of those who survived to discharge, approximately two-thirds recovered kidney function and were not receiving dialysis at discharge.

A comparative study examining differences in risk of AKI and KRT in people admitted to the hospital with COVID-19 versus seasonal influenza found that compared with seasonal influenza, COVID-19 was associated with a higher risk of AKI and KRT. COVID-19 also was associated with a higher risk of death, mechanical ventilator use, and admission to intensive care, with differences in rates of death more pronounced in patients with CKD.[27]

IMPACT OF COVID-19 ON PATIENTS WITH CKD

Although it is clear that CKD is a risk factor for developing COVID-19 AKI and is associated with adverse outcomes, the incidence of COVID-19 and the associated outcomes in people with CKD is less clear because of an underdiagnosis of CKD, particularly during the pandemic, and variation in testing for COVID-19. The impact of reductions in access to primary care services, outpatient renal clinic appointments, phlebotomy services, vascular access surgery, and delays in commencing KRT have undoubtedly had a significant impact, which, however, is difficult to quantify or measure and therefore it is difficult to truly establish the impact of COVID-19 on patients with underlying CKD.

A systematic review pooling 348 studies (382,407 participants with COVID-19 and CKD; 1,139,979 total participants with CKD) suggested that people with CKD may be at a higher risk of COVID-19 than the general population and may be at a higher risk of death than people with CKD without COVID-19.[28]

There are more data examining the incidence of COVID-19 in dialysis patients. Patients receiving dialysis were at higher risk of exposure to COVID-19 throughout the pandemic owing to the requirement of attending a health care facility regularly, often using shared transportation and exposure to other patients and health care providers. The incidence of COVID-19 therefore was significantly higher in these patients. A study from Belgium found that after standardization for age, the cumulative incidence of COVID-19 remained four times greater in patients on hemodialysis (2.54%) and 2.5 times greater in KTRs (1.60%) than in the general population.[29] In addition, outcomes after infection have been shown to be worse, with significantly higher mortality rates in patients receiving KRT than the general population.

A study using primary care data from more than 17 million people in England showed that patients with an estimated glomerular filtration rate (eGFR) in the range of 30 to 60 mL/min per 1.73 m^2 had a 33% higher risk of COVID-19–related death than those with no documented eGFR less than 60 mL/min per 1.73 m^2, even after adjustment for all recorded comorbidities. In patients with an eGFR less than 30 mL/min per 1.73 m^2, the risk of COVID-19–related death was more than 2.5-fold higher than in individuals with normal kidney function. This study also showed that patients on dialysis and recipients of a solid organ transplant had a greater than 3.5-fold increased risk of death from COVID-19 than individuals without a transplant or on dialysis.[30] Data from the Scottish Renal Registry showed high mortality rates during the first wave (26.7% in dialysis patients and 29.2% in transplant patients).[31] This decreased initially to 7% in dialysis patients and 10% in transplant patients after two vaccinations up to September 2021,[32] and further during the Omicron wave until March 2022 to 5% in dialysis patients and 2% in transplant patients, but remained considerably higher than mortality in the general population.[33]

Underlying CKD is also associated with the development of more severe COVID-19 disease. A systematic review including 21,060 patients with COVID-19 found that severe cases of COVID-19 were associated with CKD (odds ratio, 2.97; 95% CI, 1.63-5.41).[34] A large population-based cohort of more than 56 million individuals from the United Kingdom found that 1-year mortality risk was high and dependent on age, underlying conditions, CKD stage, and the incidence or prevalence of CKD, ranging from 0.5% to 37.2%. It also showed that comorbidities and multimorbidity were common, and associated with SARS-CoV-2 infection and severe COVID-19.[35] CKD rarely occurs in isolation and therefore the association with disease severity likely is driven by multimorbidity rather than CKD alone.

The most common complication of CKD is cardiovascular disease, with studies showing that cardiovascular complications are common after COVID-19. Findings from a multicenter cohort of 86,964 patients from Scotland, UK, showed that in patients with CKD, COVID-19 increased the risk of cardiovascular death by more than two-fold within 30 days (cause-specific hazard ratio meta-estimate, 2.34; 95% CI, 1.83-2.99) and by 57% at the end of the study follow-up period (cause-specific hazard ratio meta-estimate, 1.57; 95% CI, 1.31-1.89). Similarly, the risk of all-cause death in COVID-19–positive versus COVID-19–negative CKD patients was greatest within 30 days (hazard ratio, 4.53; 95% CI, 3.97-5.16). Compared with patients without CKD, those with CKD had a higher risk of testing positive (11.5% versus 9.3%). After a positive test, CKD patients had higher rates of cardiovascular death (11.1% versus 2.7%), cardiovascular complications, and cardiovascular hospitalizations (7.1% versus 3.3%) than those without CKD.[36]

VARIANTS OF CONCERN

The global spread of the SARS-CoV-2 virus has resulted in considerable genetic diversification from the original

ancestral strain.[37] Although the majority of mutations acquired are nonfunctional or detrimental to the virus, a series of viral variants have emerged over the course of the pandemic due to acquisition of genetic mutations, or combinations of mutations, which increase fitness relative to the predominant strain at the time.[37] The World Health Organization, designates them as variants of interest or variants of concern (VOC). Understanding the prevalent local VOC, and the in vitro and in vivo sensitivity to antiviral therapy, is crucial to developing effective strategies to minimize infection by vaccination and to treat infected individuals.

The emergence of SARS-CoV-2 variants to the extent that has been observed was initially unexpected because coronaviruses replicate with greater fidelity than other RNA viruses such as influenza. Emergence of novel strains has been observed in immunocompromised individuals with protracted infection, commonly immunosuppressed kidney transplant recipients who can lack both the neutralizing antibody response to prevent infection and spread of the virus within the body, and the T-cell response to clear infected cells.[38-40] VOC characteristically emerge having acquired multiple gain-of-function mutations in a rapid evolutionary jump, and immunosuppressed hosts may act as an incubator to facilitate these jumps. Cases of chronic COVID-19 infection lasting more than 150 days have been reported, and several key VOC mutations have been observed to develop independently within immunosuppressed hosts, notably the B.1.1.7 *alpha* variant that emerged early on in the pandemic in the United Kingdom.[41] Careful management of immunosuppressed patients is important from both a patient and a public health standpoint.

KIDNEY TRANSPLANT RECIPIENTS AND COVID-19

Immunosuppressed transplant recipients are a particularly vulnerable group to COVID-19. Early in the pandemic, the mortality rate for kidney transplant recipients was 29%,[42] increasing significantly with age to almost 50% in those age 75 years and older.[43] This high mortality rate likely is related to underlying comorbidities as well as the use of immunosuppressive drugs because similarly high rates were reported in dialysis patients awaiting transplantation.[44,45] Given this vulnerability, kidney transplant recipients and other immunocompromised groups were, and continue to be, prioritized for vaccination and early access to treatments.

PREVENTION OF COVID-19 IN KIDNEY TRANSPLANT RECIPIENTS

In the United Kingdom, Callaghan et al[46] reported the real-world effectiveness of the two early vaccines, the BNT162b2 (Pfizer) and the ChAdOx1-S (Astra Zeneca), in the prevention of infection and death. Compared with unvaccinated individuals, kidney transplant recipients who received two doses of vaccine had a 20% reduction in mortality risk (10.1% versus 8.1%), and no reduction in risk of infection. Furthermore, data from the Scottish Renal Registry in the United Kingdom estimated vaccine effectiveness rates for KTRs at 39% against infection and 40% against hospitalization after two doses of vaccine.[47] Although these concerning data may be related in part to differences in the severity of the original ancestral strains of SARS-CoV-2 virus, data provided from Michigan in the later Omicron VOC period showed that immunocompromised patients (rheumatologic/disease-modifying agents/steroids/transplant recipients) receiving three vaccine doses had 87% protection against the risk of hospitalization.[48] Nevertheless, the transplant population in this retrospective cohort, comprising 10% of the study population, had a hazard ratio of 3.52 for admission, indicating the importance of maintaining up-to-date vaccination.[48] Unvaccinated immunosuppressed individuals had the highest risk of COVID-19 infection.[48]

RING VACCINATION AS A STRATEGY TO PROTECT IMMUNOCOMPROMISED INDIVIDUALS

Protection of immunocompromised individuals also can be achieved by providing a lower-risk environment, by vaccination of their immediate household contacts. Immunosuppressed renal transplant recipients on standard-of-care immunosuppression (tacrolimus, mycophenolate mofetil, prednisone) had more than 1,000-fold lower IgG responses to two vaccine doses compared with their nonimmunosuppressed household controls: of the 40% of kidney transplant recipients who did respond, the antibody responses were 10-fold lower than their household contacts.[49] Taking into account pre-existing cross-reactive T-cell responses before vaccination, transplant recipients also had 10-fold lower functional T-cell responses to vaccination.[49] All household contacts showed effective neutralization of live SARS-CoV-2 virus (the gold standard correlate of protection from asymptomatic infection), suggesting that early synchronous vaccination of household contacts may limit spread of the virus to vulnerable immunocompromised individuals, an important implication for the future management of pandemics and novel variant-specific vaccines.[49]

VACCINE RESPONSE IN RENAL FAILURE AND IMMUNOCOMPROMISED INDIVIDUALS

Response to COVID-19 vaccines is impaired in individuals with kidney disease, a problem familiar to all nephrologists attempting vaccination of dialysis patients for hepatitis B or influenza. How kidney disease affects the immune response is poorly understood.

For an individual to be protected by therapeutic vaccination, the immune system needs to be able to effectively take up and process antigens to initiate an appropriate T-cell and germinal center response. The first vaccines against COVID-19 comprised nucleic acids to be translated into viral spike glycoproteins by the host rather than delivering the protein directly—technology that allowed a rapid shortening of vaccine development times. The Astra-Zeneca ChAdOx1 vaccine comprises DNA within a chimpanzee adenovirus vector. The viral vector enters host cells at the site of injection, or in draining lymph nodes, and delivers DNA into the cell nucleus, which is transcribed as messenger RNA (mRNA) and translated into protein by host machinery.[50] The Pfizer BNT162b2 and Moderna mRNA-1273 vaccines both comprise mRNA encapsulated in a lipid nanoparticle. Lipid nanoparticles are endocytosed by host cells, and release mRNA into the cell cytoplasm, which is translated by host ribosomes into spike protein.[50] These vaccines have proven to be highly effective, and induce both strong antibody and T-cell responses in healthy individuals—an achievement that has proved difficult in the development of other viral vaccines, notably influenza. Direct production of the vaccine antigen by dendritic cells has been suggested as the reason for the excellent immunogenicity observed for mRNA vaccines, by maximizing occupancy of the dendritic cell major histocompatibility complex with virus-specific peptides and thereby improving antigen-presentation to $CD4^+$ and $CD8^+$ T cells.[51]

In individuals with impaired renal function, uremia itself impairs blood dendritic cell function, and importantly for the antiviral response, plasmacytoid dendritic cell (the principal source of antiviral interferon response) function also is impaired in hemodialysis patients.[52] Thus, impairment of dendritic cell function in dialysis and transplant patients is likely to contribute to the poor vaccine response seen in these vulnerable individuals.

Additional mechanisms are likely to contribute to impaired immunity in individuals with kidney failure. CKD and type 1 diabetes are associated with poor antibody and T-cell responses to COVID-19 vaccination in Indigenous and non-Indigenous Australians, and higher rates of these comorbidities among Indigenous communities represent a barrier to effective immunity.[53] Increased concentrations of the proinflammatory cytokine IL-18 in the serum of those with comorbidities, and higher proportions of aglycosylated IgG antibody (antibodies lacking post-translational addition of sugar moieties that influence Fc receptor interaction), correlated with impaired antibody response to vaccination.[53] Although the relationship between these immune markers and impaired vaccine response in individuals with kidney disease, particularly those with CKD and type 1 diabetes, is not known, insights such as this reflect a progression toward more targeted and personalized vaccination strategies in these vulnerable groups.

As has been the experience with hepatitis B and influenza vaccinations, repeated vaccination against COVID-19, particularly with a combination of infection and vaccination (hybrid immunity), and vaccination with variant-specific bivalent vaccines, has proven effective for the majority of individuals receiving hemodialysis.[54,55]

CAN IMMUNOSUPPRESSIVE DRUG THERAPY INFLUENCE VACCINE RESPONSE IN IMMUNOCOMPROMISED INDIVIDUALS?

The classic immunosuppressive regimen used for kidney transplant patients is triple therapy, consisting of calcineurin inhibition (CNI) (tacrolimus/cyclosporin), mycophenolic acid, and prednisolone. The logical response to high mortality and poor vaccine efficacy has been the removal of the myelosuppressive component of the transplant regimen. In the absence of effective antiviral therapy, withholding mycophenolic acid in acute infection has been used clinically. Because the pathogenesis of severe COVID-19 is caused by a hyperinflammatory state (cytokine storm), addition of immunosuppressive agents has been used in transplant recipients as well as in nonimmunosuppressed individuals, including treatment with corticosteroids, anti−IL-6−receptor monoclonals, and mechanistic target of rapamycin (mToR) inhibitors.[56] With the availability of effective antivirals and monoclonal antibody treatments, immunosuppression modification is not common in the majority of cases, although the periodic emergence of antibody-escape variants means this a dynamically changing field.[57]

After the roll out of vaccines, the extent to which the immune response to vaccination was impaired in kidney transplant recipients was quickly realized.[49,58] Meaningful antibody titers and rates of seroconversion began to be achieved only with a third vaccine dose,[59] with a significant proportion of patients failing to seroconvert, and a greater proportion failing to produce an effective neutralizing antibody response, after four and five vaccine doses.[60-63] Although other immunosuppressed populations selectively lack antibody or T-cell immunity,[64-66] kidney transplant recipients on standard immunosuppression showed concomitant impairment of antibody and $CD4^+$ and $CD8^+$ T-cell immunity.[49,67]

A variety of alternative immunosuppressive therapies have been proposed to improve vaccine responses in kidney transplant recipients, from modification of patients' microbiome to immunosuppression alteration (summarized in Tables 1 and 2). As with acute infection, cessation of mycophenolate before vaccination has been trialed after reports that an antimetabolite dose is associated with failure to seroconvert.[67] Several investigations have reported improved seroconversion with

Table 1. Randomized Controlled Trials of Immunosuppression Modification to Improve COVID-19 Vaccine Response of Kidney Transplant Recipients

Study	Control	Intervention	Vaccine	Other Criteria	Sample Size	Trial ID	Evidence of Benefit?	Findings
RIVASTIM[82,83,98]	TAC MMF PRED	TAC mToRI (SIR) PRED	mRNA (original strain) third dose	Low (<100 U/mL) or nonresponder to primary course; stable graft	N = 54 (1:1)	ACTRN12621001412820	No	No difference in virus neutralization (A.2.2 or Om BA.5), T-cell response (IFNg ELISpot), or seroresponse rate (>100 U/mL RBD IgG)
Banjongjit et al[99]	TAC MPA PRED	TAC mToRI (SIR) PRED	mRNA (original strain) fourth dose	Stable graft	N = 28 (1:1)	TCTR20220404001	Yes	Improved antibody titer: 2,081 versus 4,051 BAU/mL (P = .01)
RECOVAC[7]	TAC MMF or MPA PRED	TAC PRED	mRNA (original strain) third or fourth dose	Stable graft	N = 103 (1:1)	NCT05030974	No	No significant change
RECOVAC*,[100]	TAC MMF	TAC	mRNA (original strain) second dose	Prerandomized cohort; stable graft; <80 years	N = 27	EudraCT2021-001520-18	Yes	Higher seroresponse rate (>1,000 BAU/mL): 7.7% versus 50% (P = .03 RBD IgG)
OPTIMIZE*,[70]	TAC MMF PRED	TAC mToRI (EVR) PRED	mRNA (original strain) second dose	Prerandomized cohort; stable graft	N = 32	NCT03797196	Yes	Higher seroconversion rate: 13% versus 56% (P = .009)

Abbreviations: BAU, binding antibody units; COVID-19, coronavirus disease-2019; EVR, everolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mRNA, messenger RNA; mToRI, mechanistic target of rapamycin inhibitor; Om, Omicron; OPTIMIZE, ; PRED, prednisone; RBD, receptor-binding domain; RECOVAC, REnal patients COVID-19 VACcination; RIVASTIM, rapamycin and inulin for booster vaccine response stimulation; SIR, sirolimus; TAC, tacrolimus.

*Substudy of ongoing randomized trial (prerandomized cohort).

Table 2. Planned/Ongoing Randomized Trials: WHO International Clinical Trials Registry Platform

CPAT-ISR	TAC MMF or MPA ± PRED	Immunosuppression Reduction (Unspecified)	mRNA Original/Om BA.4-5 Fourth + Dose	Low Immunity ≤2,500 U/mL; Stable Graft	N = 400 (1:1)	NCT05077254	Primary Outcome: Fold-Increase in RBD IgG Titer
PREPARE-iVAC	TAC MMF or MPA ± PRED	TAC mTORi (EVR) ± PRED	mRNA original/Om BA.4-5 fourth+ dose	Stable graft	N = 110 (1:1)	NCT05924685	Primary outcome: neutralizing antibody titer against Om BA.5
ADIVKT	Regimen includes MMF, MPA, or AZA	Reduction in MMF, MPA, or AZA	mRNA third dose		N = 50	NCT05060991	Primary outcome: change in IgG titer
BECAME[101]	TAC MMF or MPA PRED	Immunosuppression reduction (unspecified)	mRNA third dose	Seronegative; stable graft	N = 154 (1:1)	NCT04961229	Primary outcome: seroconversion of spike IgG

Abbreviations: ADIVKT, impact of immunosuppression adjustment on the immune response to SARS-CoV-2 mRNA vaccination in kidney transplant recipients; AZA, azathioprine; CPAT-ISR, COVID protection after transplant—immunosuppression reduction; EVR, everolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mRNA, messenger RNA; mTORi, mechanistic target of rapamycin inhibitor; Om, omicron; PRED, prednisone; PREPARE-iVAC, prospective randomized trial of everolimus replacing MMF/MP acid by the RECOVAC consortium to increase VACcine response in kidney transplant patients; RBD, receptor-binding domain; TAC, tacrolimus.

mycophenolate withdrawal, however, the investigations generally have lacked appropriate control groups.[68-70] A randomized controlled trial of booster vaccination of 92 seronegative kidney transplant recipients failed to show a significant effect of mycophenolate withdrawal on seroresponse rate.[71]

Clinical studies of the use of mToR inhibitors (sirolimus and everolimus) previously have suggested a beneficial effect on antiviral immunity, with lower rates of viral infection observed in the ELITE-Symphony study, Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRoliMus-based regimen (TRANSFORM) trial, and the ATHENA study relative to alternative therapies.[72-74] This observation may be the result of a relative improvement in suppression of antiviral immunity compared with an antimetabolite-containing regimen, however, significant preclinical animal studies have suggested that inhibition of mTOR complex 1 actively enhances the antiviral immune response.[75] As early as 2009, Araki et al showed enhanced $CD8^+$ memory T-cell formation and function in mice and a rhesus macaques vaccinia vaccination model.[71,76,77] Furthermore, in a human phase 2a randomized, placebo-controlled trial, a selective mTOR complex 1 inhibitor improved antibody response to influenza vaccination and decreased rates of respiratory infection in 264 elderly participants (age, >65 y) with a 6-week course of treatment.[78,79] Mannick et al suggested that this effect was the result of reversing age-associated decline in the innate antiviral interferon response, and a follow-up phase 2b/phase 3 trial was inconclusive.[80]

Separate investigations have found significantly better antibody and T-cell responses to COVID-19 vaccination in kidney transplant recipients receiving mTOR inhibitor (mTORi)-based, three-drug regimens compared with standard-of-care triple therapy. Patients receiving a regimen of CNI/mTORi/prednisone showed a greater seroconversion rate than those receiving CNI/mycophenolate mofetil (MMF)/prednisone (56% versus 38%) after primary COVID-19 vaccination, and greater virus-specific T-cell immunity by IFNg ELISpot (EUROIMMUN medizinische labor diagnostika AG, Lübeck, Germany).[81] Despite this, perivaccination immunosuppression switch from CNI/MMF/prednisone to CNI/mTORi/prednisone in a randomized controlled trial did not improve antibody or T-cell responses to a COVID-19 booster dose.[82,83]

An alternative immunosuppression protocol, mTORi/MMF/prednisone, also was associated with a greater seroconversion rate after primary COVID-19 vaccination compared with standard triple therapy (80% versus 28%), and a remarkable 12-fold greater antiviral T-cell response by IFNg ELISpot.[82] Furthermore, participants receiving sirolimus as a component of their immunosuppression had a significantly greater T-cell response than healthy individuals, both in total frequency of virus-specific $CD4^+$ and $CD8^+$ effector and central memory T cells and in frequency of multifunctional antiviral T cells, supporting mTOR inhibition as a potential strategy to actively boost cellular immunity to vaccination.[82] Thus, although strategies used in randomized trials to date (namely mycophenolate to mTORi switch) have not shown a clear benefit, there are compelling observational and preclinical data supporting the effect of mTORi on the T-cell memory response, which may be imparted by an optimized immunosuppression modification strategy.

TREATMENT OF COVID-19 INFECTION IN THE PRESENCE OF RENAL FAILURE AND IMMUNOSUPPRESSION

A variety of antiviral agents and passive immunization strategies have been developed to treat COVID-19 −infected individuals.[84] Antiviral agents are required to be administered early in the course of the disease, and hence early diagnosis once symptoms have developed is essential in management.

Nirmatrelvir + ritonavir, available in combination therapy, is an oral agent with activity against COVID-19, and has multiple serious interactions with immunosuppressive agents and in general should not be given to transplant patients unless under direct supervision of a transplant unit. Nirmatrelvir is an oral protease inhibitor with direct antiviral activity against B.1.672 (Delta) VOC. In a large retrospective study from Israel performed during the Omicron VOC surge, 10,777 immunosuppressed patients (881 treated; 9,896 controls) were studied. This population also included 1,471 chronic kidney failure patients (85 treated, 1,346 controls).

In the older immunocompromised population (age >65 y), hospitalization was reduced in those receiving nirmatrelvir (14.7 per 100,000 compared with 58 per 100,000 in the control population). The adjusted hazard ratio for death was 0.21 (95% CI, 0.05-0.82). No benefit was seen in younger patient populations.[85]

Remdesivir is an intravenous RNA-dependent RNA polymerase inhibitor of coronaviruses. Remdesivir when given early for 3 days IV administered as an outpatient to high-risk vaccinated recipients was effective and reduced hospitalization by 75% and respiratory failure by 95%.[86]

Tixagevimab and cilgavimab are two monoclonal antibodies that bind to two distinct epitopes on the SARS-CoV-2 spike protein. This combination has a prolonged half-life and therefore is attractive as therapy for immunocompromised individuals such as transplant recipients. Importantly, it retained activity against some of the VOC. In a large prospective trial it was shown to be effective as pre-exposure prophylaxis.[87] The trial included a small component of individuals receiving immunosuppressive therapy. However, a real-world

study from Benotmane et al[88] showed that although the combination had some benefit, neutralization was greater in individuals who had contracted COVID-19 infection. Pre-exposure prophylaxis with tixagevimab and cilgavimab in solid organ transplant recipients was studied in a retrospective cohort study from Boston. In vaccinated KTRs, SARS-CoV-2 infection was 1.8% in those receiving tixagevimab/cilgavimab compared with 4.7% in controls.[89] Finally, tixagevimab and cilgavimab for pre-exposure prophylaxis was assessed in a large cohort of immunocompromised patients during the Omicron wave in France.[90] Less than 5% subsequently developed COVID-19, with low rates of severe illnesses in those infected.

Other antibodies against COVID-19 also have been developed, including sotrovimab, a humanized neutralizing antibody with activity against COVID-19, was indicated for patients with positive polymerase chain reaction, immune compromise, and symptoms. Data from the OpenSAFELY platform in the United Kingdom showed that in the routine care of adult patients in England with COVID-19 in the community, at high risk of severe outcomes from infection, those receiving sotrovimab had a substantially lower risk of severe COVID-19 outcomes than those treated with molnupiravir when omicron BA.1 and BA.2 were the predominant variants.[91] Similar findings were shown in patients undergoing KRT in the United Kingdom.[92]

IMPLICATIONS OF LONG-COVID ON KIDNEY HEALTH

There have been an increasing number of studies examining the longer-term effect of COVID-19 on the kidney. Re-infection with SARS-CoV-2 has been shown to further increase risk of death, hospitalization, and sequelae including pulmonary, cardiovascular, hematologic, diabetes, gastrointestinal, kidney, mental health, musculoskeletal, and neurologic disorders in an analysis of a large cohort from the Veterans Affairs' US national health care database.[93] Another study also using the US Veterans Affairs' database found that beyond the first 30 days of infection, those who survived COVID-19 showed increased risk of AKI, renal function decline, end-stage kidney disease, and Major Adverse Kidney Events with the risks of kidney outcomes increasing according to the severity of the acute infection and present even in those without AKI in the acute phase.[94] A study from China also showed that in patients without AKI and preserved kidney function, 107 of 822 had developed renal impairment, with an eGFR of less than 90 mL/min per 1.73 m^2 at 6 months.[95] Furthermore, another study from China with a median follow-up period of 342 days found that eGFR reduction from acute phase to follow-up evaluation was 8.30% (95% CI, 5.99-10.61) higher among AKI participants than in those without AKI after multivariable adjustment. Participants with AKI had an odds ratio of 4.60 (95% CI, 2.10-10.08) for reduced renal function at follow-up evaluation. The percentage of eGFR reduction for participants with AKI stage 1, stage 2, and stage 3 was 6.02% (95% CI, 3.48-8.57), 15.99% (95% CI, 10.77-21.22), and 17.79% (95% CI, 9.14-26.43) higher compared with those without AKI, respectively.[96]

The Hamburg City Health Study COVID-19 program showed that subjects who apparently recovered from mild to moderate COVID-19 infection (mostly nonhospitalized individuals) had signs of subclinical multiorgan damage. A total of 443 (the majority of which were nonhospitalized) individuals were examined for a median of 9.6 months after the first positive COVID-19 test and matched for age, sex, and education, with 1,328 controls from a population-based German cohort. eGFR based on creatinine measurements was reduced in patients after COVID-19 infection by 2.35 mL/min per 1.73 m^2 (95% CI, −4.04 to −0.67; adjusted $P = .019$).[97]

CONCLUSIONS

The COVID-19 pandemic has significantly impacted and continues to impact kidney health, leading to both acute and longer-term adverse outcomes in patients across the whole spectrum of CKD, including patients receiving dialysis and KTRs. Although vaccination programs and emerging treatments have led to significant improvement in outcomes, these patients remain extremely vulnerable with evolving evidence regarding the longer-term impact of the virus.

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