

# Kidney Transplantation and COVID-19

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## INTRODUCTION

Kidney transplantation is the treatment of choice for patients with advanced chronic kidney disease or end stage kidney disease. More than 1,500,000 people live with a transplanted organ worldwide. In the United States, approximately 40,000 patients received an organ transplant in 2019 with almost 60% of those receiving a kidney transplant.<sup>1</sup> Generally, kidney transplant recipients receive induction therapy (antithymocyte globulin, basiliximab or alemtuzumab) at the time of transplant, followed by a maintenance immunosuppressive protocol consisting of prednisone, a calcineurin inhibitor (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus), and an antimetabolite (mycophenolic acid, azathioprine). Long-term immunosuppression is associated with an increased risk of infectious complications and specifically, transplant recipients are more susceptible to infections resulting from ribonucleic acid respiratory viruses.<sup>2</sup>

The enduring epidemic outbreak originating in Wuhan, China in December 2019 caused by the 2019 novel coronavirus (COVID-19) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created a dangerous and deadly public health disaster of international proportions. Although this outbreak has raised great concern among the general population, its specific impact on transplant recipients is unknown. The Centers for Disease Control and Prevention (CDC) lists immunocompromised patients, including those requiring immunosuppression following renal transplantation, as at high-risk for developing severe disease from COVID-19.

## WHY KIDNEY TRANSPLANTATION SLOWED DOWN OR STOPPED DURING THE PANDEMIC

Due to the “uncertainty” of patient outcomes within the transplant community, transplantation volumes declined during the early period of the COVID-19 pandemic. In early April of this year, the United Network for Organ Sharing (UNOS) released data showing that transplantation rates in the US dropped sharply coincident with the timing of

stringent infection control measures. There was a 51.1% reduction in deceased donor kidney transplantation and 71.8% of centers placed a complete suspension of live donor kidney transplantation.<sup>3</sup> Furthermore, 84% of transplant centers added stringent restrictions included transplanting only highly sensitized patients, those with a negative cross-match, higher acuity patients and those without dialysis access.<sup>3</sup> Some centers reported transplanting only healthier recipients with the best quality organs and with the lowest risk of delayed graft function because of fears of overwhelming the health-care system that was already being stretched thin by the pandemic. Because of concerns of the sensitivity of the RT-PCR test and the fear of transmitting COVID-19 from the donor to the recipient, the decision to proceed with transplantation was made on a case-by-case basis, after careful assessment of the risks and benefits of transplantation. For this reason, rates of deceased donor discard and waiting list inactivation increased dramatically while the rate of new additions to the waiting list decreased during the pandemic. Using data from the National Organ Procurement Agency in France and the UNOS in USA, Loupy et al. showed that the trend in declining transplant rates accelerated over time from February 2020 until April 2020, with the reduction driven primarily by kidney transplantation. There was a 90.6% overall reduction in deceased donor kidney transplantation in France and 51.1% in the USA during this time period, although a substantial negative effect was also seen for heart, lung and liver transplants.<sup>4</sup> An analysis of US registry data showed that between March 15 and April 30, 2020, the numbers of deceased donor and live donor kidney transplant procedures were, respectively, 24% and 87% lower than would be expected based on pre-epidemic data.<sup>5</sup>

## HOW TO MANAGE IMMUNOSUPPRESSIVE MEDICATIONS IN KIDNEY TRANSPLANT RECIPIENTS (KTRS) INFECTED WITH COVID-19

Because of their chronically immunosuppressed status, KTRs are at increased risk for infectious complications, accounting for significant morbidity and mortality. Infections rank as the second leading cause of death in these individuals.<sup>6</sup> Additionally, KTRs frequently suffer from medical conditions such as diabetes, hypertension, cardiovascular disease and chronic kidney disease that have been identified

as risk factors for adverse outcomes from COVID-19.<sup>7</sup> However, little is known about the true risk, presentation, and outcome of COVID-19 in KTRs. Furthermore, the optimal management of a solid organ transplant recipient with COVID-19 is not clearly determined. Reducing immunosuppression may not only lead to acute rejection but may result in an immune reconstitution-like reaction with paradoxical worsening of the infection.

Early reports of outcomes in kidney transplant patients with COVID-19 originated in Europe since the pandemic spread from Wuhan to this continent before spreading to the rest of the world. These are limited predominantly to case series and single-center studies and are lacking in control groups of non-transplant patients. Regardless, observational studies can provide useful early insights into effective treatment strategies. Alberici et al<sup>8</sup> described the early experience of COVID-19 infections among 20 Italian KTRs. Management consisted of the withdrawal of all immunosuppression followed by the administration of hydroxychloroquine (95%), lopinavir/ ritonavir (79%) and the administration of methylprednisolone (16 mg) in all patients. Additionally, six patients who deteriorated clinically were given tocilizumab. In this limited cohort, the development of COVID pneumonia was associated with a high risk of clinical deterioration. ICU level care was required in 20% of patients accompanied by a high rate of acute allograft injury (30%) and a mortality rate of 25%. The UK experience was summarized by Banerjee et al,<sup>9</sup> describing the clinical course of 7 KTRs infected with COVID-19. Modifications in the immunosuppressive regimen consisted of withdrawal of the antimetabolite and reducing the tacrolimus dose, while prednisone was kept unchanged or increased. 57% of patients required ICU admission and were otherwise managed with supportive care alone. In this cohort, older and diabetic patients were at higher risk for poor outcomes, with elevated D-Dimer, ferritin and troponin levels clinically predictive of case severity. In their series, 57% of patients developed acute kidney injury with mortality rate of 14%.

In early March of this year, New York City became the epicenter of the coronavirus pandemic in the United States. At Montefiore Medical Center, Akalin et al<sup>10</sup> summarized the course of 36 KTRs with COVID infection during the outbreak in New York City between March 16 and April 1, 2020. Seventy-five percent of affected individuals were recipients of deceased donor kidney transplants and maintenance immunosuppressive regimen consisted of tacrolimus, MMF and prednisone. Most patients suffered from medical comorbidities including hypertension (94%), diabetes (69%), a history of smoking or active smokers (36%) and heart disease (17%). Management consisted of the withdrawal of the antimetabolite in most patients (86%) and tacrolimus (21%) in severely ill patients. Eighty-six percent of patients received hydroxychloroquine and 2 patients received tocilizumab. Allograft outcomes were poor with 21% of patients

requiring renal replacement therapy. The study showed a high early mortality rate of 28% at 3 weeks. In another study from New York during the first three weeks of the outbreak (March 13 to April 3, 2020), Pereira and colleagues described the outcomes of COVID-19 infections in ninety patients with solid organ transplants which included 46 KTRs.<sup>11</sup> Many patients had comorbidities associated with COVID-19 severity, such as obesity, cardiovascular disease, and chronic kidney disease. Seventy six percent required hospitalization and 35% required mechanical ventilation. As per previous studies, immunosuppressive medications were reduced (88% antimetabolite, 7% steroid and 18% CNI decreased or held). Ninety-one percent of patients received hydroxychloroquine, 66% azithromycin, 3% remdesivir, 21% tocilizumab, and 24% bolus steroids. The overall mortality rate was 18%. Twenty-four percent of hospitalized patients and 52% of those who were admitted to the intensive care unit died during the 3-week study period.

The outcome of COVID-19 in elderly transplant patients was described by Crespo et al.<sup>12</sup> From March 12 until April 4, 2020, COVID-19 was diagnosed in 16 of 324 KT patients aged  $\geq 65$  years old (4.9%) in their cohort. Up to 33% showed renal graft dysfunction with short-term fatality rate of 50% at a median time of 3 days following admission. Those who died were more frequently obese, frail, and had underlying heart disease. The study is alarming for the early and high mortality rate among the elderly kidney transplant population infected with COVID-19.

#### WHAT IS THE ROLE OF TOCILIZUMAB AND REMDESIVIR IN TREATING KTRS WITH COVID-19?

As the cytokine storm triggered by the coronavirus may be responsible for severe manifestations of COVID-19, immunosuppressive therapy could potentially mitigate some of these effects and reduce the risk of developing complications. Therefore, interleukin-6 (IL-6) targeting therapies have been proposed to manage the acute respiratory distress syndrome and organ dysfunction when present. Perez-Saez et al<sup>13</sup> published their multicenter cohort experience using tocilizumab, a monoclonal antibody directed against the IL-6 receptor, in 80 KTRs in Spain with COVID-19. The mortality rate was high at 32.5% with a predilection for older patients ( $> 60$  YO). Of note, 10% of treated patients developed superimposed bacterial infection after tocilizumab infusion. IL-6 and other inflammatory markers, including LDH, ferritin, and D-dimer increased early after tocilizumab administration and correlated with poor patient survival. CRP was the only marker that decreased within 72 hours after tocilizumab administration and was associated with improved outcomes. The authors found no difference in respiratory improvement at 72 hours following Tocilizumab infusion between survivors and non-survivors. Non-survivors were more severely ill at presentation and

received tocilizumab more frequently in the intensive care unit. The authors concluded that declining CRP levels after tocilizumab administration together with clinical and radiological response might help to identify patients with favorable outcomes. In contrast, 2 case reports describing the use of tocilizumab in 2 KTRs infected with COVID-19 showed rapid resolution of the cytokine storm and favorable clinical course without the need of mechanical ventilation<sup>14,15</sup>, suggesting that earlier treatment in the disease course may be beneficial. Larger randomized controlled trials are clearly needed to confirm the utility and safety of IL-6 inhibition in treating KTRs with COVID-19.

Remdesivir is a nucleoside analogue prodrug that has been shown to have inhibitory effects on pathogenic animal and human coronaviruses, including COVID-19 in vitro. On May 1, 2020, the Food and Drug Administration (FDA) issued an emergency use authorization for this anti-viral agent for treatment of severe COVID-19 patients. The preliminary results of a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with COVID-19 have recently been published, documenting faster recovery time (11 vs 15 days) and reduced mortality by 14 days in the treatment arm.<sup>16</sup> To date, no similar trials have been conducted in solid organ recipients and its value in treating COVID-19 in this cohort remains to be determined.

### CASES AT RHODE ISLAND HOSPITAL

The Transplant Program at Rhode Island Hospital (RIH) experienced 16 kidney transplant recipients infected with COVID-19 between March 1 and May 18, 2020. Of these, three had previously failed their allografts with return to renal replacement therapy, although all remained on immunosuppressive therapy at the time of infection. All three were subsequently taken off their immunosuppression following confirmed infection and did well without hospital admission or additional adjunctive therapy. Of the 13 active KTRs infected with COVID-19, 2 patients transplanted more than 10 years previously were managed as outpatients and 11 KTRs required hospitalization. The median age of the cohort was 54 years with the majority being female (62%). Immunosuppressive medications were reduced in 12 of 13 patients by discontinuation of the antimetabolite followed by a reduction in the calcineurin inhibitor dose. Interestingly, tacrolimus or sirolimus levels were noted to be supratherapeutic in 67% of patients on hospital presentation, which was likely due to increased drug absorption from COVID-induced diarrhea or decreased drug metabolism resulting from hepatic dysfunction. Adjunctive therapy consisted of remdesivir (36%), convalescent plasma (46%) and tocilizumab (27%). IL-6 levels were markedly elevated (>1,000) in 3 KTRs. There was a single mortality, involving the only patient treated with hydroxychloroquine. Of note, hydroxychloroquine was not commonly used at RIH as a

treatment regimen while extremely elevated levels of IL-6 were common compared to the other studies. All 3 patients who received tocilizumab survived with one patient developing superimposed bacterial infection with graft pyelonephritis and ESBL bacteremia. Convalescent plasma was well tolerated in the four patients treated and subsequent publications have since shown that convalescent plasma could help patient recovery from COVID-19,<sup>17-19</sup> prompting emergency use approval by the FDA as a potential treatment option.

### CLINICAL OUTCOMES

Current reports suggest that kidney transplant recipients show similar symptoms but worse outcomes when compared to the general population. Indeed, results from the TANGO International Transplant Consortium from the US, Italy and Spain identified 144 hospitalized adult kidney transplant recipients infected with COVID-19 and showed high rates of acute kidney injury (51%) and mortality (32%) among this cohort with non-survivors being older and having higher IL-6 levels.<sup>20</sup> This outcome is similar to previous single-center reports discussed here, which observed death rates between 14% and 30%. Of note, this and previously published studies focusing on solid organ transplant patients lacked comparison with a control group to ascertain their risk as compared to a general population. To address this knowledge gap, Molnar and colleague compared outcomes in solid organ transplant (SOT) recipients versus non-SOT patients with COVID-19 who were admitted to intensive care units throughout the US, using data from a multicenter cohort study.<sup>21</sup> Using a propensity score-matched cohort, the authors showed that death within 28 days of ICU admission was similar in SOT and non-SOT patients (40 and 43% respectively, respectively) and showed that there was no difference between groups in the duration of ICU length of stay, risk of ARDS, secondary infection, thromboembolic events, or receipt/duration of invasive mechanical ventilation. The authors suggested that the higher use of corticosteroids treatment in SOT compared to non-SOT patients may have contributed to this favorable outcome. Furthermore, they hypothesized that immunosuppressive medications may have mitigated pro-inflammatory cytokine activation in SOT patients, which might result in a lower risk of developing cytokine-release syndrome.

### CONCLUSIONS

As the COVID-19 pandemic continues to progress, we are likely to see an increasing number of kidney transplant recipients who will be exposed to and subsequently develop a COVID-19 infection. However, the current management of COVID-19 disease in kidney transplant recipients remains ill-defined. No randomized controlled trials have

been conducted to assess how immunosuppression should be managed during acute infection nor how they should be resumed after remission. COVID-19 is associated with a higher mortality rate in KTRs than the general population with particularly poor outcomes noted in elderly kidney transplant population. Given the high mortality rate, transplant clinicians should focus on primary prevention with a careful case-by-case assessment of risk versus benefits of continuing immunosuppression in those infected. It seems rational to reduce the immunosuppressive load with first step being the withdrawal of antimetabolite agents followed by a reduction or discontinuation of the calcineurin inhibitor. Several agents have been used for treating KTRs infected with COVID-19 although none have shown proven efficacy. Ultimately, studies with a larger number of patients and longer follow-up are required to better assess the optimal management, outcomes, and treatment of kidney transplant recipients with COVID-19 infection.

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