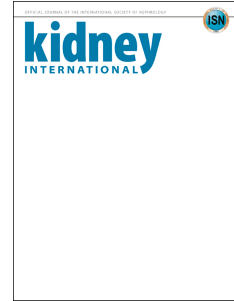


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P Toby Coates, Germaine Wong, Tilman Drueke, Brad Rovin, Pierre Ronco

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Early Experience with COVID-19 in Kidney Transplantation

By

P Toby Coates, Germaine Wong, Tilman Drueke, Brad Rovin and Pierre Ronco for the Editors

P. Toby Coates
Royal Adelaide Hospital
Renal and Transplantation Services
Level 9 East Wing
North Terrace
Adelaide
South Australia
5000
Australia
Toby.Coates@sa.gov.au

In this edition of *Kidney International*, we publish two series of kidney transplant patients during the Covid-19 pandemic, which have taken different approaches to transplant immunosuppressive therapy and anti-viral treatment in the early days of the developing pandemic in the United Kingdom and Italy. The first series of 7 cases of COVID-19 infection in kidney transplant recipients comes from St Georges University Hospital in south London, UK (1) and the second series of 20 cases originates from Spedali Civili University Hospital in Brescia, Italy (2). The general opinion regarding viral susceptibility in transplant recipients based on previous experience is that immune compromised individuals are at greater risk of severe infection because of an impaired immune system, particularly among those with concurrent comorbidities. There is a lack of information about the impact of the COVID-19 infection on kidney transplants, despite over 800,000 global cases being reported worldwide to date. Now Banerjee and co-authors (1) provide a real world experience of managing 7 kidney transplants during the developing COVID-19 pandemic. Overall, two of these recipients were managed on an out-patient basis, the other five required hospital admission; four in intensive care units and one patient died. This experience has some important clinical messages for transplant recipients and for transplant programs. Firstly, the successful home management for COVID-19 positive patients in the community provides some reassurance that some milder kidney transplant cases may be successfully managed without hospitalization. Secondly, two of these reported cases were transplanted with 3 months of the pandemic being declared, and thus provide experience of clinical outcomes during the period of maximal medical immunosuppression (1). Case 3 was transplanted in December 2019, before the first case of COVID-19 was reported in the UK (January 2020),

and presented on the 10th of March at a time when 373 COVID-19 cases had been reported. This case developed severe respiratory disease requiring ongoing ventilation and became anuric. Case 5 was transplanted on the 29th of February when the UK had recorded 20 cases, and then presented on the 13th of March when 797 COVID-19 cases had been recorded. In this case the graft has been maintained without severe respiratory involvement and the need for ventilation. During the period from December 2019 until mid-March 2020 the St Georges unit performed 32 transplants. Importantly in these patients from the UK, the immunosuppressive management was predominantly reduction and general supportive therapy without specific anti-viral therapeutics.

In the second series of clinical cases from Brescia, Italy, a contrasting approach was taken to the management of 20 COVID-19 infected kidney transplant patients with SARS-Cov-2 pneumonia. In this series by Alberici and colleagues, all patients had baseline immunosuppression withdrawn (2). In 19/20 cases methylprednisolone 16mg daily was added and anti-viral therapy (lopinavir/ritonavir, darunavir/ritonavir or darunavir/cobicistat) and hydroxychloroquine commenced. In a subgroup of 6 patients, the humanized anti interleukin-6 (IL-6) receptor monoclonal antibody tocilizumab was also added (see table 2 and supplementary material for details). The choice of lopinavir/ritonavir was made to target viral replication in combination with hydroxychloroquine which was added to help reduce viral replication. Dexamethasone and tocilizumab, given to counter cytokine storm, were felt to be critical in the ARDS seen with COVID-19 infection. Despite these impressive, seemingly logical therapeutic interventions and use of supportive antibiotics (noting that azithromycin was not given as has been suggested by others to be essential in combination with hydroxychloroquine) the clinical outcomes for the transplant

patients were poor with 25% mortality mainly due to complications from pneumonia. The renal outcomes for the transplant kidneys included 6 cases of AKI and 1 case requiring haemodialysis. Furthermore the use of this complex combination of agents in critically ill patients is not also without risks since prolongation of the cardiac QTc interval by both hydroxychloroquine and lopinavir/ritonavir have been reported. More importantly, a recently published trial of lopinavir/ritonavir found no significant benefits in terms of viral clearance and survival between the treatment and the no treatment arms. Moreover, both anti-viral agents interact with calcineurin inhibitors causing marked inhibition of metabolism and potential high readings. So what can we take from these first fascinating reports? Firstly the investigators should be congratulated for initiating a bold logical yet different anti-viral strategies very early on in the pandemic, allowing the transplant world to see the first results of anti-viral therapy in immunocompromised transplant patients. While the current evidence is largely extrapolated from observational data and case series, the novel clinical experience with anti-IL-6, which was applied in worsening respiratory cases by Alberici provided some potential hope that this strategy might be helpful in the future and could be a potential component for future trials. However, the approach of aggressive immunosuppression withdrawal and anti-inflammatory combination of drugs did not achieve the survival benefits we would have hoped for. By contrast, the smaller series from the UK with more gentle immunosuppression reduction and no anti-inflammatory drugs still had poor outcomes (14% mortality), but two patients were managed in the community with this approach. The use of hydroxychloroquine in the Italian series did not seem to provide any additional benefit compared to those in the UK series. Of note, the first reported kidney transplant recipient in the world from WuHan (3) also underwent immunosuppression minimization and kept the transplant.

Unfortunately many confounding and selection biases, not least of which is the small sample size in both studies, does not allow us to draw firm conclusions from these fascinating first experiences. Other strategies including switch therapies from tacrolimus to cyclosporine (with its known *in vitro* anti-viral effect) are potential avenues for future exploration.

However taken together these important early experiences underscore the increased risk to recipients of kidney transplantation during the developing pandemic and strongly support the decision to suspend transplantation programs (where possible) except for exceptional cases. Sharing clinical experience with these cases is crucial and the editors of Kidney International would like to inform our readers of the link to The International Transplantation Societies round up of COVID-19 responses <https://tts.org/txicovid19> .

The clinical management of kidney transplant patients with COVID-19 infection will clearly vary with clinical presentation and with growing experience from transplant units worldwide. Randomized trials will likely be impossible in this situation and therefore publishing cases and international efforts to gather information and develop a data repository from around the world will provide the information the field needs to move forward safely after this pandemic finishes.

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