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COVID-19 infection in kidney transplant recipients

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OPEN

By 21 March 2020 infections related to the novel coronavirus SARS-CoV-2 had affected people from 177 countries and caused 11,252 reported deaths worldwide. Little is known about risk, presentation and outcomes of SARS-CoV-2 (COVID-19) infection in kidney transplantation recipients, who may be at high-risk due to long-term immunosuppression, comorbidity and residual chronic kidney disease. Whilst COVID-19 is predominantly a respiratory disease, in severe cases it can cause kidney and multi-organ failure. It is unknown if immunocompromised hosts are at higher risk of more severe systemic disease. Therefore, we report on seven cases of COVID-19 in kidney transplant recipients (median age 54 (range 45-69), three females, from a cohort of 2082 managed transplant follow-up patients) over a six-week period in three south London hospitals. Two of 32 patients presented within three months of transplantation. Overall, two were managed on an out-patient basis, but the remaining five required hospital admission, four in intensive care units. All patients displayed respiratory symptoms and fever. Other common clinical features included hypoxia, chest crepitation, lymphopenia and high C-reactive protein. Very high D dimer, ferritin and troponin levels occurred in severe cases and likely prognostic. Immunosuppression was modified in six of seven patients. Three patients with severe disease were diabetic. During a three week follow up one patient recovered, and one patient died. Thus, our findings suggest COVID-19 infection in kidney transplant patients may be severe, requiring intensive care admission. The symptoms are predominantly respiratory and associated with fever. Most patients had their immunosuppression reduced and were treated with supportive therapy.

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The novel coronavirus 2019 (or coronavirus disease 2019 [COVID-19]) infection, which originated in the city of Wuhan, in Hubei province, China, in December 2019 shares close similarities in its genomic structure with the severe acute respiratory syndrome coronavirus (SARS-CoV) that caused the SARS global pandemic in 2003 and the Middle East respiratory syndrome (MERS) epidemic in 2012 (MERS-CoV), and even closer similarities to bat SARS-like betacoronavirus (bat-SL-CoVZC45 betacoronavirus) and bat-SL-CoVZXC21.[1,2]

Between December 31, 2019, and March 27, 2020, 532,692 COVID-19 cases and 24,077 deaths worldwide have been identified as being caused by a newly identified enveloped RNA virus named SARS-CoV-2.[3] In the United Kingdom, between January 31, 2020, and March 20, 2020, 3983 cases were identified with 177 (4% of tested patients) deaths.[4] Due to widespread nature, COVID-19 was declared as a pandemic by World Health Organization on March 11, 2020, and 176 countries are affected as of March 27, 2020.[3]

The SARS pandemic was reported to affect both pediatric and adult kidney transplant

Table 1 | Clinical characteristics and outcome of 7 kidney transplant patients with COVID-19 infection

Patient	Age/sex	Tx date	Comorbidities	Respiratory and renal involvement	Baseline creatinine (eGFR ml/min per 1.73 m^2)	Baseline immunosuppression and treatment	ACEI or ARB	Outcome
1	48/M	1989	HT	No	350 (15–18)	Aza/Pred No change	No	Stayed at home, full recovery
2	67/F	03/2019	T2D/HT	Yes, ARDS + AKI (CVVH)	150 (45)	Tac/MMF/Pred MMF stopped	Yes ACEI	Died
3	54/F	12/2019	PTDM/CMV	Yes, ARDS + AKI (CVVH)	132 (48)	Tac/MMF/Pred Tac and MMF stopped	No	Alive, ventilated
4	65/M	08/2018	Wheelchair/ HTN	No ARDS	180 (23)	Tac/MMF/Pred MMF stopped	No	Alive, in medical ward
5	69/F	02/2020	DM/HT	No ARDS AKI	165 (31)	Tac/MMF/Pred MMF stopped	No	Brief ITU stay, not intubated; stepped down to ward
6	54/M	05/2013	Hemolytic anemia/HT	No ARDS	187 (47)	Tac/MMF MMF stopped	No	Stayed at home, still has cough and some flu-like symptoms
7	45/M	09/2017 (2nd Tx)	HT	No ARDS AKI (HD)	450 (12–16)	Tac/Aza/Aza Aza stopped Tac dose reduced	No	Admitted, managed in the ward; severe AKI

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; Aza, azathioprine; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CVVH, continuous venovenous hemofiltration; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; F, female; ITU, intensive therapy unit; M, male; MMF, mycophenolate mofetil; Pred, prednisolone; PTDM, posttransplant diabetes mellitus; T2D, type 2 diabetes; Tac, tacrolimus; Tx, treatment(s).

recipients in Hong Kong, with less severe disease in the pediatric population.[5] One liver transplant patient died with the SARS-CoV infection in 2003.[6] The MERS coronavirus infection had a variable impact on kidney transplant recipients. In 1 report of 2 kidney transplant patients, one died of progressive respiratory disease and acute kidney injury while the other survived.[7] To the best of our knowledge, only 1 patient with kidney transplantation has been reported in the literature who suffered from COVID-19 infection in Wuhan, China, and improved 13 days after hospital admission.[8] The 63-year-old kidney transplant recipient presented with fever, chest pain, cough, low lymphocyte, high serum C-reactive protein (CRP), and abnormal chest computed tomography scan on February 2, 2020. Tacrolimus and mycophenolate administration was discontinued. He was treated with oxygen, methyl prednisolone, umifenovir, moxifloxacin, biapenem, i.v. Ig, inhaled interferon-α, and pantoprazole. He made a successful recovery and was discharged on day 13.

We report here the first 7 cases of COVID-19 in kidney transplant recipients in south London hospitals.

CASES

We have seen 7 cases of kidney transplant recipients with proven COVID-19 infection in south London in March 2020. These patients are described herein, and their main characteristics are summarized in Tables 1 and 2.

Patient 1

A 48-year-old man with deceased donor kidney transplant in 1989 with failing transplant kidney (estimated glomerular filtration rate [eGFR]: 15–18 ml/min per 1.73 m^2) called the

Table 2 | Blood parameters during COVID-19 infection

Patient	White cell count (× 10^9/l) (3.5–10)	Lymphocyte count (× 10^9/l) (1–3.5)	Serum CRP (mg/l) (<5)	Serum ferritin (μg/l) (25–200)	Serum D dimer (μg/l) (0–500)	Serum LDH (U/l) (100–240)	Serum troponin I (ng/l) (<34)
1	—	—	—	—	—	—	—
2	6 (D1)	0.8 (D1)	83 (D1)		2032 (D3), >6000 (D10)	1226 (D10)	78 (D1), 395 (D10)
3	11.25 (D1)	0.5 (D1)	329 (D1)	—	—	—	—
4	—	—	—	—	—	—	—
5	9.4 (D1)	0.3 (D1)	—	—	—	—	30 (D4)[a]
6	10 (D1)	4.0 (D1)	—	—	—	—	—
7	5.5 (D1)	0.3 (D1)	198 (D1)	6919 (D3)	1907 (D3)	502 (D3)	35 (D7)

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; D, day after admission and D1 is day of admission; LDH, lactate dehydrogenase.
[a]Serum troponin T (0–14 ng/l).

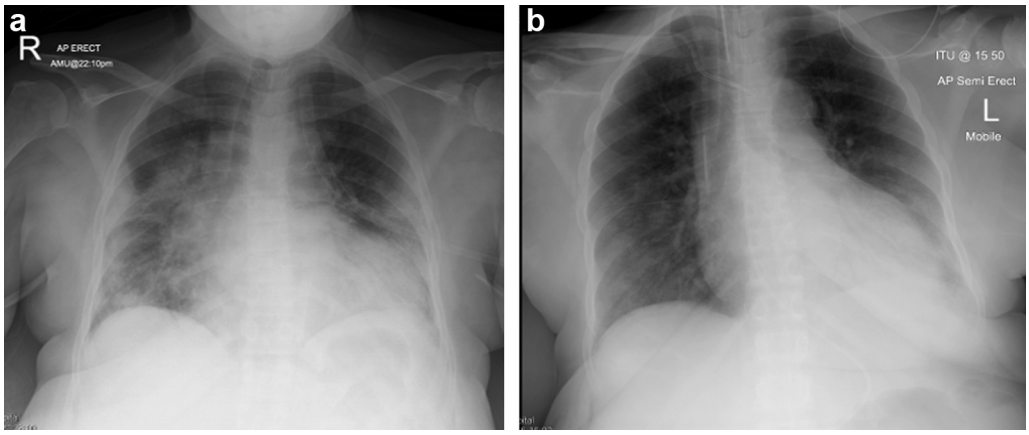

Figure 1 | Case 2: Chest X-ray (a) on admission showing bilateral patchy consolidation and (b) 8 days later showing improvement in lung infiltrates.

National Health Service (111) helpline in the first week of March 2020 with cough, fever, and mild shortness of breath. He tested positive for COVID-19 by nose and throat swabs taken on March 2. As he was clinically well, he was asked to stay at home and self-isolate. His immunosuppression was azathioprine 75 mg once a day (OD) and prednisolone 5 mg OD, which was not changed. He was not on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker at the time of presentation. He has made a full recovery. The transplant kidney function remained stable.

Patient 2

A 67-year-old woman with insulin-dependent type 2 diabetes and end-stage kidney disease on hemodialysis therapy for 4 years received a deceased donor kidney transplant in March 2019. Her eGFR was 45 to 55 ml/min per 1.73 m^2. She was maintained on tacrolimus with levels between 5 and 8 ng/ml, mycophenolate mofetil (MMF) 250 mg twice a day (BD), and prednisolone 5 mg OD. Her other medications included ramipril, aspirin, alfacalcidol, and amiloride. She presented on March 5 with cough, fever, and shortness of breath. Chest X-ray revealed bilateral patchy consolidation (Figure 1a). SARS-CoV-2 RNA polymerase chain reaction tests from nose and throat viral swabs were positive. Bronchial washing for pneumocystis polymerase chain reaction was negative, as was blood polymerase chain reaction for cytomegalovirus DNA. There was no other positive microbiological diagnosis. She was hypoxic with peripheral oxygen saturation of 86% and a respiratory rate of 26 breaths/min, so she was transferred to intensive therapy unit (ITU) and commenced noninvasive ventilation (continuous positive airway pressure for type 1 respiratory failure) and subsequent intubation and ventilation as her clinical condition deteriorated. Serum CRP on admission was 83 mg/l, hemoglobin 110 g/l, with normal total white cell count, and mild lymphopenia (lymphocyte count 0.8 × 10^9/l). She was treated with broad spectrum antibiotics. No specific antiviral drugs were given. MMF was ceased. Low-dose tacrolimus was initially continued but stopped 1 day before death. On day 3 post admission, she developed acute kidney injury (AKI), with a serum creatinine increase to 225 μmol/l. She remained stable on the ventilator with reducing oxygen requirements and improvement in lung infiltrates on chest X-ray (Figure 1b) but deteriorated markedly on March 16 with high serum lactate and lactate dehydrogenase levels and an acute rise of CRP to 190. She developed severe metabolic acidosis resistant to correction on continuous venovenous hemodiafiltration, probably owing to an intra-abdominal event (bowel infarction and/or intra-abdominal sepsis). She deteriorated rapidly and died on March 17.

Patient 3

A 54-year-old woman with a history of adult polycystic kidney disease, end-stage kidney disease in 2012, was on hemodialysis for 7 years, and received a deceased donor kidney transplant in December 2019. Soon thereafter, she experienced an episode of cytomegalovirus infection and developed posttransplant diabetes mellitus. Her medications included BD doses of tacrolimus 11 mg and MMF 500 mg and OD doses of prednisolone 5 mg, amlodipine 5 mg, aspirin 75 mg, bisoprolol 2.5 mg, co-

trimoxazole 480 mg, doxazosin 2 mg, isoniazid 300 mg, omeprazole 20 mg, pyridoxine 25 mg, and gliclazide 120 mg and 80 mg. Three months after deceased donor kidney transplantation, on March 10, she presented with shortness of breath to the emergency department. On initial assessment, her oxygen saturations were 60% with heart rate of 105 beats/min and blood pressure of 190/99 mm Hg. She was started immediately on continuous positive airway pressure and her oxygen saturations improved to 87%. Auscultation of the chest revealed widespread crepitations and her chest X-ray showed bilateral pulmonary infiltrates (Supplementary Figure S1A). She was found to be positive for SARS-CoV-2 RNA. Her cytomegalovirus, adenovirus, and other respiratory viral screen along with atypical pneumonia serologies were negative. There was no other positive microbiological diagnosis. She developed features of acute respiratory distress syndrome and AKI (creatinine 242 μmol/l, baseline 132 μmol/l).

Her respiratory status rapidly deteriorated in the emergency department and she required intubation 8 hours later and continues to be ventilated currently. MMF was stopped on March 10 and tacrolimus on March 16. Broad spectrum antibiotics and antiviral, oseltamivir were administered. She was also empirically treated for pneumocystis with high dose co-trimoxazole. Serum CRP decreased from 329 mg/l on day of admission to 169 mg/l 7 days later. She became anuric and started continuous venovenous hemofiltration, which continues. Her latest chest X-ray showed some resolution of the pulmonary infiltrates (Supplementary Figure S1B).

Patient 4

A 65-year-old wheelchair-bound man, with a history of hypertensive nephrosclerosis and recurrent thromboembolic events developed end-stage renal disease in 2014 and received a deceased donor kidney transplant in August 2018. Seventeen months after kidney transplantation, he presented to hospital with shortness of breath and chest pain and was admitted to ITU. He was diagnosed with COVID-19 infection on March 15. MMF was stopped and he currently continues with tacrolimus and prednisolone. He was discharged from the ITU and is currently admitted to a medical ward still requiring 4 to 6 L oxygen to maintain saturations. Kidney function remained stable.

Patient 5

A 69-year-old woman with long-standing diabetes, hypertension, and end-stage kidney disease was on peritoneal dialysis therapy since 2012 and hemodialysis therapy since 2014; she received a deceased donor kidney transplantation on February 29 and was discharged on March 9. Her immunosuppressive treatment included tacrolimus, MMF, and prednisolone. Other medications included insulin, amlodipine 10 mg, ezetimibe 10 mg, levothyroxine 150 μg, co-trimoxazole 480 mg, as well as doxazosin 4 mg BD, and clonazepam 1 mg as needed. She presented with shortness of breath, fever (39 °C), diarrhea, and vomiting on March 13. Her chest X-ray showed shadowing of left base on March 13 that worsened on March 19 (Supplementary Figure S2A and B). She tested positive for SARS-CoV-2 RNA on March 14, 2020. She was unwell with oxygen saturation of 82% and blood pressure 166/52 mm Hg. Oxygen saturation improved to 97% with 4 l oxygen by nasal cannula. Hemoglobin was 74 g/l, serum N-terminal prohormone of brain natriuretic peptide 5186 ng/l, and serum fibrinogen 4.2 g/l. Her lymphocyte count decreased on day 3 of admission to 0.3×10^9/l and has remained low. Tacrolimus was continued, and MMF was held from March 14. She was treated initially with doxycycline, piperacillin-tazobactam, paracetamol, furosemide, and blood transfusion. She was moved to ITU on March 15 for respiratory support but did not need more than 5 l/min oxygen and transferred back to ward on March 17. On March 20, her serum creatinine was 138 μmol/l. She remains an inpatient and is being managed in a general ward.

Patient 6

A 54-year-old man with urate nephropathy and past history of hereditary hemolytic anemia received a kidney transplant 7 years ago. He presented on March 10 with cough and fever (38.5 °C) and tested positive for SARS-CoV-2 RNA on March 13. He was adequately hydrated, and his vitals were stable. He received paracetamol and continued his usual medications including Advagraf (Astellas Pharma Europe, Leiderdorp, the Netherlands) 3.5 mg OD, MMF 500 mg BD, nifedipine 30 mg OD, atorvastatin 30 mg at night, bisoprolol 10 mg OD, ramipril 10 mg OD, doxazosin 8 mg BD, alfacalcidol 1 μg OD, and penicillin 250 mg OD. He developed AKI with a rise in creatinine from 145 μmol/l to 187 μmol/l. Hemoglobin was 141 g/l. Blood cell counts are shown in

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Table 2. He remained symptomatic on March 21 with cough and mild fever. As the symptoms were not resolving, MMF was stopped, and he has managed to stay at home.

Patient 7

A 45-year-old man with a failing, second kidney transplant from September 2017 presented with fever, flu-like symptoms, cough for 7 days, and shortness of breath for 1 day. He had arterial hypertension with no other comorbidities. He was a sensitized recipient with panel reactive antibodies at 90% and therefore, was maintained on long-term triple immunosuppression: tacrolimus, azathioprine (switched in late 2018 from MMF due to gastrointestinal side effects), and prednisolone 10 mg OD. On admission on March 17, he was tachypneic and hypoxic with oxygen saturation of 90% on room air, which was corrected to >95% on 4 l/min oxygen through nasal cannula. Nasal and throat swabs were positive for SARS-CoV-2 RNA. He developed AKI with serum creatinine 967 μmol/l and eGFR 5 ml/min per 1.73 m^2 (baseline creatinine: 400–450; baseline eGFR: 12–16). He was lymphopenic with lymphocyte count of 0.3 × 10^9/l (baseline: 1–1.2 × 10^9/l) with normal hemoglobin and white cell count. Liver function tests were normal on admission, but alanine aminotransferase went up to 138 U/l on day 4. Chest X-ray revealed bilateral infiltrates (Supplementary Figure S3). Azathioprine was stopped on admission, tacrolimus reduced, and prednisolone increased to 15 mg OD. So far, he needed 1 hemodialysis session. He is recovering from respiratory point of view and as of March 23, 2020, the oxygen saturations are >95% on 2 l/min. He remains hemodynamically stable.

DISCUSSION

In this report we discuss our first 7 cases of COVID-19 infection in kidney transplant recipients from south London, United Kingdom. Median age of transplant recipients was 54 years (range, 45–69 years) comprising 4 men, 3 women. Of 7 patients, 2 were managed on an outpatient basis and stayed at home, with the remaining 5 (71%) requiring hospital admission. Four among the latter required ITU admission, and 1 is being managed in the renal ward. Of 4 patients sent to ITU, 2 needed intubation and ventilation; the other 2 were managed with oxygen through mask and noninvasive ventilation only. There was 1 death in this small series of 7 patients (mortality rate of 14%). All 3 patients with severe disease were female and also had diabetes. Two patients presented within 3 months of kidney transplantation (1 within 2 weeks) while kidney transplant vintage was 12 months or more in the remaining 5 cases. The patients were managed in 3 centers and the total number of prevalent transplant patients in these centers was 2082, with 32 patients transplanted from December 15, 2019, to March 15, 2020, during the developing pandemic.

Transplant patients are at higher risk due to immunosuppression, underlying chronic kidney disease, and other comorbidities, in particular diabetes and hypertension, which are now recognized as significant factors that influence outcomes in patients with COVID-19 infection.[9] Three of our patients had chronic kidney disease stage 4 to 5, with 1 recovering at home and 1 requiring hospital admission but recovering without needing ITU admission. The remaining 4 patients had chronic kidney disease stage 3, of which 2 had severe disease requiring intubation and ventilation and 1 of them died. Both patients who had severe COVID-19 including the one who died had diabetes mellitus.

Managing immunosuppression in these patients is challenging and should take into account age, severity of COVID-19 infection, associated comorbidities, and time posttransplant. In transplant patients with mild to moderate infections, the usual practice is to continue or make reductions in the dose of immunosuppressive drugs, but this approach might favor high mortality in patients admitted to hospital with COVID-19 infection. While we acknowledge that firm recommendations are not possible based on the small sample size of this study, we suggest that antiproliferative agents (MMF and azathioprine) should be stopped at the time of admission to hospital, dose of prednisolone should be either unchanged or increased, and tacrolimus dose should be reduced. In severe infections (requiring intubation and ventilation), an argument can be made for stopping calcineurin inhibitors completely while maintaining corticosteroid therapy. The role of cytokine storm and inflammation due to antiviral immune response as a driver of severe respiratory disease and acute respiratory distress syndrome has been discussed since the outbreak of this disease in December 2019, prompting trials of anti-interleukin 6 monoclonal antibody tocilizumab and case for continuing steroids in

infected patients. A similar argument can be made for continuing low-dose tacrolimus, but more evidence is needed before drawing firm conclusions. An obvious concern is risk of rejection with reduction in immunosuppression but given the high mortality rate of COVID-19 infection in hospitalized patients, clinicians should focus on keeping their patients alive with a careful case-by-case assessment of risks versus benefits of continuing immunosuppression. With regard to induction treatment, it is likely that lymphocyte-depleting antibodies increase the risk; therefore, many centers in the United Kingdom have stopped performing transplants requiring induction with either antithymocyte globulin or alemtuzumab. All patients in this series received basiliximab induction therapy at time of transplantations. Five of the 7 patients presented here were receiving triple immunosuppression. Two patients with mild illness who did not require hospital admission and recovered fully at home were on dual immunosuppression (1 on azathioprine plus prednisolone and 1 on tacrolimus plus MMF).

With regard to concomitant therapy with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, in line with current UK Renal Association and European Society of Cardiology recommendations, these therapies were not discontinued.

One of our 7 patients died, which is a mortality rate of 14%, although it is too soon to comment on likely mortality rates in this group of patients. Two of our patients presented within 3 months after transplantation and 1 presented within 2 weeks. UK National Health Service Blood and Transplant Organ Donation and Transplantation have since produced guidelines on COVID-19 screening in deceased donors and the transplant units are risk stratifying donors and recipients before considering kidney transplantation. Transplantation is a high-risk procedure during this pandemic due to the risk of transmitting COVID-19 infection from the donor to the recipient as well as risk of recipient developing severe disease under higher levels of immunosuppression in the first 3 months posttransplant. We suggest that apart from carefully selecting donor-recipient pairs, transplantation is not advisable during this pandemic, especially for older recipients with comorbidities, in particular diabetes. We have stopped performing living donor transplants and are in discussions to suspend deceased donor program. In addition to significant concerns about the effect of COVID-19 on immunosuppressed patients, increasing worries about access to ITU in the coming weeks and redistribution of staff to critical care to provide support for increasing number of COVID-19 patients, it is likely that deceased donor program will be suspended within most of the UK centers soon.

AKI has been described with COVID-19 infections in up to 15% patients, and occurrence of proteinuria or hematuria has been reported. In our series, the observation that 4 of 7 patients had AKI (57%) may be an early signal that transplant patients are at higher risk of AKI with COVID-19 infection, compared with 29% AKI in critically ill patients of general population in Wuhan, China.[11] Angiotensin-converting enzyme 2 and dipeptidyl peptidase, which are expressed in proximal tubule cells,[12,13] have been identified as receptors for SARS-CoV and MERS-CoV. Uptake of SARS-CoV-2 virus into the proximal tubular epithelium is a possible explanation for AKI.

With regard to prognostic blood tests including lymphocyte counts and serum levels of D dimer, ferritin and troponin are likely to be valuable. Four of 5 patients who required admission had lymphopenia, whereas the 2 who did not need admission had normal lymphocyte counts. As many patients on immunosuppression are likely to have baseline lymphopenia, a further drop in lymphocyte count is likely to be of prognostic value. In our patient who died, both D dimer and troponin levels were elevated on day 3 post admission with further marked increase (in particular D dimer) later during the course of her illness. In the absence of any obvious thromboembolic events, this suggests microvascular thrombosis or disseminated intravascular coagulation with possible gut ischemia. Very high ferritin and D dimer levels were also noted in the case for patient 7 of our series. We suggest that D dimer, ferritin, and troponin should be measured in all patients with severe COVID-19 infection on admission and subsequently in those who are not showing clinical improvement.

In 2 of our patients, the lung infiltrates showed significant improvement without any specific antiviral treatment 7 to 9 days post admission. The patient who died is among them and was improving from the respiratory point of view. She died of an abdominal complication and the clinical diagnosis was

possible bowel infarction or intra-abdominal sepsis. Based on this observation, we would like to highlight that the mortality in critically ill patients with COVID-19 infection could be due to extrapulmonary complications such as myocarditis or bowel involvement.

With regard to specific antiviral therapies, although a recent trial showed no benefit of lopinavir-ritonavir in hospitalized patients with severe COVID-19, it remains possible that treatment with these drugs as well as hydroxychloroquine will be considered in patients with COVID-19 pneumonia.[14] The choice of calcineurin inhibitor may also have a role to play. Thus, for instance, cyclosporin A has been shown to have an inhibitory effect on proliferation of corona viruses and hepatitis C virus *in vitro*, while this is not the case for tacrolimus. Cyclosporin A is thought to inhibit the replication of a diverse array of coronaviruses through its impact on cyclophilin A and B.[15,16] While this needs further exploration, we do not think switching to cyclosporine A from tacrolimus can be recommended at this stage for transplant patients with COVID-19 infection.

In conclusion, in this first series of 7 renal transplant patients infected with SARS-CoV-2, 1 recipient died (14%) and significant AKI was observed. Lymphopenia, very high ferritin and D dimer levels, and raised troponin levels are seen in severe disease and may be of prognostic value. These tests should be part of routine testing in kidney transplant patients requiring hospital admission for COVID-19 infection. We suggest suspending kidney transplantation during the COVID-19 pandemic particularly for high-risk older recipients with comorbidities. Rigorous adherence to hand hygiene, recommended isolation procedures, and regular assessment—virtually and/or telephonically—of transplant patients will help reduce the incidence and facilitate management of mild-to-moderate cases in the community as we could in 2 of our 7 patients described.

The COVID-19 UK register has been set up by the UK transplant registry held by Organ Donation and Transplantation to record all cases of renal transplant patients presenting with COVID-19 infection and analysis of registry data will help clinicians make informed decisions about management of these complex patients in these uncertain and rapidly evolving times.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Case 3: CxR (**A**) on admission, showing bilateral patchy consolidation, and (**B**) 9 days later showing improvement in lung infiltrates.

Figure S2. Case 5: CxR (**A**) on admission showing left basal shadow that (**B**) is worsening to B/L patchy consolidation 6 days later.

Figure S3. Case 7: CxR on admission showing bilateral lung infiltrates.

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