An early experience of COVID-19 disease in pediatric and young adult renal transplant recipients

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Abstract

**Background:** COVID-19 is caused by a novel form of coronavirus known as SARS-CoV-2. Patients can present with a wide variety of symptoms from fever to severe respiratory distress. Immunocompromised patients, including solid organ transplant recipients, may present with atypical symptoms, making the diagnosis of COVID-19 more difficult to make. New reports have been emerging about the management of COVID-19 disease in adult renal transplant recipients. However, very little is known in pediatric renal transplant recipients.

**Methods:** Here, we describe a case report of four pediatric renal transplant recipients who presented with mild-to-moderate COVID-19 disease.

**Results:** All patients presented with upper respiratory infection symptoms, with one requiring hospitalization for hypoxia. Patients were treated mostly with supportive care. Two of the patients developed AKI which resolved four to eight weeks after illness. All four patients developed COVID IgG antibodies one to two months after becoming infected.

**Conclusion:** This case series demonstrates that immunocompromised renal transplant recipients have comparable outcomes compared with immunocompetent children.

**KEYWORDS**
COVID-19, pediatrics, renal transplant

1 | BACKGROUND

COVID-19 is caused by a novel form of coronavirus known as SARS-CoV-2. Primarily a respiratory disease, there is a wide range in presentation from mild symptoms including headaches, anosmia, myalgias, sore throat, emesis, and diarrhea to devastating respiratory failure. In immunocompromised patients, COVID-19 can present with atypical symptoms and often multiple co-infections. Adult patients requiring chronic immunosuppression, such as patients who have received a SOT, are at high risk of morbidity and mortality from COVID-19. Although children were thought to be relatively spared from significant mortality and morbidity, pediatric SOT recipients remain at high risk of contracting respiratory viral infections. There are few case reports of adult SOT recipients and sparse information about COVID-19 disease in pediatric SOT, specifically in pediatric kidney transplant recipients. Here, we report four pediatric kidney transplant recipients with mild-to-moderate COVID-19 disease.

2 | CASE REPORTS

2.1 | Patient #1

Patient #1 is a 21-y/o female with past medical history significant for ESKD secondary to C3 glomerulopathy, now with a living donor renal transplant from her sister in 2015. Her maintenance
immunosuppression consisted of mycophenolic acid 360 mg BID and tacrolimus 2 mg BID.

She initially presented to the ED with four days of fever (Tmax 101.5°F), headache, cough, mild dyspnea, back pain, and decrease in fluid intake without decrease in UOP. She had been in contact with a family member found to be SARS-CoV-2 positive. In the ED, she was febrile, with normal oxygen saturations on room air, and had otherwise normal vital signs. She was clinically well-appearing with a normal physical examination. SARS-CoV-2 NP swab was found to be positive. As she was clinically well, she was discharged from the ED.

She was followed closely by her primary nephrologist via telemedicine. Six days after her initial ED visit, she was noted to have persistent fevers, shortness of breath, dyspnea on exertion, and oxygen saturations to the low 90s as determined by a family member’s pulse oximetry. Given her worsening respiratory distress, it was advised she proceed to the ED. In the ED, she was noted to be febrile to 101.4°F, hypoxic to 88%, and tachypneic with a respiratory rate of 30. CXR showed bilateral patchy consolidations. She was admitted to the inpatient floor for management of respiratory distress. She required up to 4 liters of oxygen the first night of her admission. She developed mild leukopenia and lymphopenia (3.6 k/mm3 and 13.4%, respectively), which resolved the following day. Serum creatinine remained at baseline of 0.8 mg/dL. She was started on hydroxychloroquine and ceftriaxone as per protocol at that time. Her mycophenolic acid was held, and tacrolimus dose was decreased to 1.5 mg BID to maintain trough levels between 4-6 ng/mL. While admitted, she remained on hydroxychloroquine with EKG monitoring every other day. Due to her improved respiratory status, she did not receive remdesivir.

Prior to discharge, she had been afebrile and on room air without any dyspnea for 48 hours. Her mycophenolic acid was then restarted. Two months after active infection, she tested COVID IgG antibody positive.

2.2 | Patient #2

Patient #2 is a 15 y/o female with past medical history significant for ESKD secondary to FSGS, now status post a deceased donor kidney transplant in 2008. She has had a complicated post-transplant course including early recurrence of FSGS which entered remission with plasmapheresis. Her maintenance immunosuppression consisted of mycophenolic acid 250 mg BID, sirolimus 1.5 mg daily, and prednisone 5 mg daily.

She presented with mild cough, congestion, and decrease in fluid intake for three days and two days of fever (Tmax of 101.2 °F). She denied any decrease in UOP, hematuria, or dysuria. Her mother had been ill with COVID-19 symptoms two weeks prior. Upon initial presentation to the ED, patient was well appearing. Vitals were within normal limits with normal oxygen saturation on room air. CBC did not have leukopenia or lymphocytopenia. BMP was notable for mild metabolic acidosis (18 meq/L) and AKI with a rise in serum creatinine to 1.34 mg/dL from a baseline of 1.0 mg/dL. CRP was elevated to 12 mg/dL. SARS-CoV-2 NP swab was positive. As she was well appearing, she was discharged home. Mycophenolic acid was held, and she was continued on sirolimus (goal trough level between 4-6 ng/mL) and prednisone. She was followed closely through telemedicine. Her mycophenolic acid was reintroduced after she was noted to be afebrile for 48 hours. Serum creatinine gradually normalized to baseline when checked at eight weeks after the onset of illness. One month after illness, she was COVID IgG antibody positive.

2.3 | Patient #3

Patient #3 is an 18 y/o male ESKD secondary to congenital malformation of the urinary tract, now status post a preemptive living-related donor renal transplant in 2012. Post-transplant course was complicated by BK nephropathy. His maintenance immunosuppression consisted of mycophenolic acid 720 mg twice a day and sirolimus 2 mg once a day. He presented to our telemedicine clinic after having two days of fever (Tmax of 102°F) along with anosmia, mild cough, and weakness. Patient was evaluated in the ED and was noted to be febrile, tachycardic, and hypertensive with a normal oxygen saturation. He endorsed adequate fluid intake and adequate UOP. There were no known sick contacts. CBC was within normal limits. BMP demonstrated serum creatinine to 1.3 mg/dL and elevated from his baseline of 1.0 mg/dL. CXR demonstrated questionable subtle round opacities in the midlung fields. He was found to be SARS-CoV-2 NP swab positive. As he was clinically well appearing without respiratory distress and tolerating fluids by mouth, he was discharged from the ED with close follow-up. Given his COVID diagnosis and CXR finding, maintenance immunosuppression was minimized by decreasing his mycophenolate acid dose to 360 mg BID. He was kept on sirolimus with goal trough levels between 4 and 6 ng/mL.

He was seen for follow-up via telemedicine. At that time, his fevers and cough had resolved 3 days after his initial ED visit (for a total of 6 days of fever). Mycophenolic acid dose was then increased to 720 mg BID. Serum creatinine normalized four weeks after initial diagnosis. His COVID IgG was found to be positive two months after initial COVID infection.

2.4 | Patient #4

Patient #4 is a 9 y/o male with past medical history significant for ESKD secondary to posterior urethral valves, now status post a preemptive living-related donor kidney transplant in 2018. Post-transplant course was relatively unremarkable. His current immunosuppression consisted of tacrolimus 2.0 mg in the AM and 1.5 mg in the PM and mycophenolate mofetil 250 mg twice a day. He presented to his primary care physician with mild upper respiratory symptoms without fevers. His sick contacts included his mother (positive SARS-CoV-2 NP swab) and siblings. His SARS-CoV-2 NP swab was found to be positive. As he had mild
symptoms, no changes were made to his immunosuppression regimen. His serum creatinine remained at his baseline of 0.7 mg/dL. He was seen for follow-up one month later and remained well-appearing without significant changes in his laboratory findings. His COVID-19 IgG was found to be positive when tested two months after initial disease.

### DISCUSSION

At the time of publication, this case report is one of the first to report multiple cases of COVID-19 in pediatric renal transplant recipients. It is thought that pediatric patients, including transplant recipients, fare better than the adult patients.\(^5,^9\) The case fatality rate in the general population has been reported to range from 1% to 6%, and mortality in the adult renal transplant patient has been reported to range from 14% to 28%.\(^2,^4,^7\) Currently, in the literature, there are few case reports of COVID-19 in pediatric renal transplant patients, all of whom had mild disease, similar to the findings seen in our case report.\(^10-12\) A brief overview of the clinical characteristics including COVID-19 symptoms in our transplant recipients is summarized in Table 1. Laboratory findings, treatment, and outcomes of our transplant patients with COVID-19 disease can be found in Table 2.

AKI, defined as an increase in creatinine by more than 0.3 mg/dL, was noted in two out of four of our transplant recipients with COVID-19, similar to other pediatric reports (Table 2).\(^7,^11\) None of our patients required renal replacement therapy. AKI in COVID-19 patients has been thought to be multifactorial secondary to both prerenal (ie, dehydration) and intrinsic renal causes.\(^13\) In smaller case series of pediatric renal transplant patients, three of the patients had prerenal AKI, while the other had AKI secondary to tacrolimus toxicity.\(^10,^11\) In our case series, we speculate that the AKI is likely multifactorial including prerenal AKI from dehydration, acute tubular necrosis, underlying decreased renal reserve, and direct effect of COVID-19. However, this is speculation as kidney biopsies were not performed on our two patients. Recent reports suggest that COVID-19 may also cause intra-renal manifestations as COVID-19 has been found within the urine of infected patients postulating that SARS-CoV-2 directly attacks the kidney.\(^14,^15\) This has also been evident through renal biopsies of patients with COVID-19 which have demonstrated various findings such as severe acute tubular necrosis with lymphocyte and macrophage infiltration, peritubular erythrocyte aggregation, glomerular fibrin thrombi with ischemic collapse, microangiopathy, membrane attack complex within tubules indicative of complement activation, and collapsing glomerulopathy.\(^12\) Our patients did not require renal replacement therapy, suggesting that the pathophysiology of AKI may differ between age groups. In all of our patients, AKI had resolved.

As with any infection in immunosuppressed patients, assessing immunosuppression is a key component of the treatment regimen. Based on studies from other viral infections, it is thought that for patients with severe COVID-19 disease requiring mechanical ventilation and ICU admission, antiproliferative agents and calcineurin inhibitors should be discontinued and glucocorticoid therapy increased. However, in those with mild symptoms, antiproliferative therapy should be discontinued while calcineurin inhibitors and glucocorticoid therapies are continued.\(^7,^8\) In our case series, the reduction in immunosuppression was based on the degree of clinical symptoms (Tables 1 and 2). Patients who were referred to the ED or those requiring hospitalizations had changes to their immunosuppression. This included reduction in their anti-metabolite medication with lower trough levels of their calcineurin or mTOR inhibitors. If the patient was afebrile for at least 48 hours with improvement in their respiratory symptoms, immunosuppression was increased to maintenance doses. Of note, patient #1 was started on hydroxychloroquine prior to the release of studies demonstrating the ineffectiveness of the medication. Interestingly, DSA testing two to six months after initial disease did not demonstrate new DSA formation in spite of being exposed to this novel virus along with changes in immunosuppression. All of our patients following their COVID-19 disease have remained clinically well.

Patient #2 was noted to be positive for the virus one month after presentation. It would be interesting to identify how many of these

| Patient #1 | Patient #2 | Patient #3 | Patient #4 |
|-----------|-------------|------------|------------|
| Sex | Female | Female | Male | Male |
| Age, years | 21 | 15 | 18 | 9 |
| Ethnicity | Caucasian | X | | |
| Hispanic | X | | | |
| Time since transplant, years | 5 | 12 | 8 | 2 |
| Diabetic donor renal transplant | | | | X |
| Hypertension | | | | X |
| Diabetes mellitus | | | | |
| Body mass index, kg/m\(^2\) | 29 | 28.1 | 23.5 | 24.6 |
| COVID-19 symptoms | | | | |
| Fever | X | X | X | |
| Chills/Myalgias | X | X | | |
| Anosmia | | | | X |
| Congestion | X | X | X | |
| Dyspnea | X | | | |
| Cough | X | X | X | X |
| Sore throat | | | | |
| Abdominal pain/Diarrhea | | | | |
| Positive contact with COVID-19 | X | X | X | |
patients remain NP swab positive, as this was seen in other pediatric renal transplant recipients. The estimated median time from initiation of symptoms to a negative PCR was noted to be 11 days. This raises the question of whether their immunocompromised state predisposes these patients in having difficulty with clearing the virus. This is highlighted by reports of prolonged SARS-CoV-2 in feces of patients on steroids compared with those not on steroids (20 days vs 11 days, respectively, p value < 0.01). Although the validity of COVID IgG antibodies is not known yet, it is interesting that these immunosuppressed patients were still able to mount an antibody response. All our patients tested for COVID IgG antibodies were found to be positive.

Our case series is in concordance with other case series which report that patients on immunosuppression appear to have a mild COVID-19 clinical course which is similar to immunocompetent children. Although our patients presented with similar symptoms to the general population, we still need to be mindful that chronically immunosuppressed patients may present with atypical symptoms. The patients with mild clinical symptoms were successfully managed at home with close follow-up achieved using telemedicine. Our case series is small and mostly represents adolescents and young adults, making it difficult to apply our findings to all of pediatric renal transplantation. There are many questions that remain to be answered, including optimizing treatment strategies as well as what long-term follow-up will hold. Hopefully, this case report in conjunction with other future multi-centered pediatric studies will enlighten the trajectory of this novel disease.

** AUTHORS’ CONTRIBUTION**

Sonia Solomon: Conceptualized or designed the work and drafted the article; Sonia Solomon, Tanya Pereira, and Dmitry Samsonov: Critically revisited the article and involved in final approval of the version to be published.

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How to cite this article: Solomon S, Pereira T, Samsonov D. An early experience of COVID-19 disease in pediatric and young adult renal transplant recipients. *Pediatr Transplant*. 2021;25:e13972. [https://doi.org/10.1111/petr.13972](https://doi.org/10.1111/petr.13972)