Received: 24 December 2021 | Revised: 1 February 2022 | Accepted: 18 February 2022

DOI: 10.1111/ctr.14623

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

LETTER TO THE EDITOR

SARS-CoV-2 infection in pediatric kidney transplant recipients

Emerging evidence from adult patients suggests that transplant recipients, who are immunosuppressed, may be at increased risk of a more severe outcome related to Coronavirus disease of 2019 (COVID-19). Some reports, however, suggest that children have a relatively mild course of disease and have better outcomes when compared with adults.[1,2] Furthermore, some studies found that pediatric immunosuppressed patients with SARS-CoV-2 infection had a similar prognosis to immunocompetent children.[3,4] Nevertheless, the outcomes of COVID-19 in pediatric kidney transplant (KT) recipients remain largely unclear.

In our centre, between March 2020 and March 2021, five cases (9%) of COVID-19 infection were identified in a cohort of 55 paediatric KT recipients. In Portugal, the main variants during this period were 20A, 20B, 20E (EU1) and 20I (Alpha, V1), according to local data. The main results are listed in Table 1. Median age at diagnosis of COVID-19 infection was 13 years and four were females. All had family epidemiological links of COVID-19 infection. Median time after KT at COVID-19 diagnosis was 38 months (1 month-11 years) and the median follow-up after COVID-19 infection was 2 months (2–9 months). All patients underwent deceased-donor KT. Cardiovascular disease was the most common comorbidity present in all five patients, but none had lung disease, diabetes, dyslipidaemia, or obesity. One patient was asymptomatic. The remaining four patients had mild disease, with symptoms like fever, headache, myalgias, cough and rhinorrhoea, without respiratory distress or hypoxemia. Two patients had acute allograft dysfunction, with no change in urine output, but with a slight creatinine rise (22% and 30%), which returned to baseline after infection resolution and oral hydration. No imaging studies were performed. None needed hospital admission. There were no cases of allograft loss. All patients maintained a close follow-up during illness and recovery period, and none had paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS). All were on maintenance immunosuppression with glucocorticoids, mycophenolate mofetil and tacrolimus, according to local protocol. The treatment during COVID-19 infection was only supportive, with no need to reduce immunosuppression. All had measurable antibody response at 3–6 months after COVID-19 infection with anti-spike S1 protein and receptor-binding domain antibodies of 102 to >2500 U/ml (laboratory reference range: positive if ≥ 0.8 U/ml).

An ongoing international survey initiated by the European Rare Kidney Disease Reference Network and supported by international pediatric nephrology societies suggests that the incidence of COVID-19 in pediatric KT recipients is similar to the incidence of COVID-19 in the general paediatric population.[5] Moreover, currently available evidence suggests that immunosuppressed children with KT are not at increased risk of severe COVID-19 disease.[2–4] The reasons for milder disease in children remain obscure, but are probably multifactorial, such as cross-reactive immunity with other human coronaviruses, different distribution and functioning of viral receptors, healthier respiratory tracts and decreased prevalence of comorbidities. Furthermore, the iatrogenic immunosuppression provided after KT might contribute to diminish the innate immune response and hence reducing COVID-19 severity.

PIMS affects predominantly previously healthy school-age children. In our center, 14 patients with PIMS were admitted during the time of follow-up of this study, but none of them were on immunosuppressive treatment.

The management of immunosuppression, duration of viral shedding, and antibody production in pediatric KT recipients with SARS-CoV-2 infection are largely unknown. All our cases had post-infection measurable antibody response 3 or 6 months after COVID-19 infection.

There are currently no evidence-based reports to support specific adjustments to immunosuppressive medications in relation to COVID-19. It must be emphasized that the decision to continue or discontinue any immunosuppression lies with the clinician, guided by local guidelines, with consideration of their potential benefit versus their ongoing immunosuppressive effect. Although reduction of immunosuppression at the time of active infection is reasonable, it may not be necessary as the pulmonary injury is thought to be due to the "cytokine storm" leading to excessive activation of the host innate immune inflammatory response. Hence, being immunosuppressed may actually be of advantage as this may cause minimal to no lung and extra pulmonary tissue damage.[5]

In our series, the presentation of COVID-19 in KT recipients was no different from the general pediatric population; the treatment during COVID-19 infection was exclusively supportive, with no immunosuppression reduction; and there was an excellent outcome. Despite the small sample size, these results support that symptomatic treatment in pediatric KT recipients with mild or asymptomatic COVID-19 infection might be sufficient. We believe that the risk of allograft loss outweighs the unknown benefits of the reduction of immunosuppression in mild COVID-19 in pediatric KT recipients.

TABLE 1 Characteristics of the five KT recipients with COVID-19 infection[a]

Median age (minimum, maximum)	13 years (7–16 years)
Gender, *n* (%)	Female: 4 (80%)
Type of transplant, *n* (%)	Deceased-donor transplant: 5 (100%)
Underlying kidney disease, *n* (%)	Steroid-resistant nephrotic syndrome: 2 (40%)
	Renal tubular dysgenesis: 1 (20%)
	Nephronophthisis: 1 (20%)
	Unknown: 1 (20%)
Comorbidities, *n* (%)	Hypertension: 5 (100%)
	Hyperuricemia: 2 (40%)
	Left ventricular hypertrophy: 1 (20%)
	Patent arterial duct surgically treated: 1 (20%)
	Mild aortic regurgitation: 1 (20%)
Baseline immunosuppression, *n* (%)	Glucocorticoids, mycophenolate mofetil and tacrolimus: 5 (100%)
Median time after KT at COVID-19 diagnosis (minimum, maximum)	38 months (1 month-11 years)
Median follow-up after COVID-19 (minimum, maximum)	2 months (2–9 months)
Signs and symptoms, *n* (%)	Fever: 2 (40%)
	Cough: 2 (40%)
	Rhinorrhoea: 2 (40%)
	Myalgias: 2 (40%)
	Headache: 2 (40%)
	Sore throat: 1 (20%)
	Diarrhoea: 1 (20%)
	Anosmia: 1 (20%)
	Asymptomatic: 1 (20%)
Laboratory findings, *n* (%)	Lymphopenia (<1000/mcL): 2 (40%)
	Thrombocytopenia (<150.000/mcL): 1 (20%)
Median eGFR in ml/min/1.73 m^2 (minimum, maximum)	Baseline eGFR: 102.6 (63.2–212.8)
	eGFR at COVID-19 diagnosis: 99.1 (48.8–174.8)
Allograft outcome, *n* (%)	Acute dysfunction: 2 (40%)
	Graft loss: 0 (0%)
Hospital admission, *n* (%)	None (0%)
COVID-19 infection treatment, *n* (%)	Supportive treatment only: 5 (100%)
	Other: none (0%)
COVID-19 total antibody response, *n* (%)	5 (100%)

[a]All COVID-19 cases were identified by a polymerase chain reaction test for SARS-CoV-2 in nasal and oropharyngeal swab.

ACKNOWLEDGMENTS

None. There was no external funding for the preparation of this paper.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by *Clinical Transplantation*.

AUTHORS CONTRIBUTION

Ana Dias Curado: data analysis and interpretation, drafting of the article, bibliographical search. Ana Zagalo: drafting of the article, bibliographical search. Filipa Durão: research design, critical reviewing of the content of the article. Patrícia Costa-Reis: critical reviewing of the content of the article. Ana Rita Sandes: critical reviewing of the content of the article. José Eduardo Esteves da Silva: critical reviewing of the content of the article. Rosário Stone: critical reviewing of the content of the article.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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