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Pediatric transplantation during the COVID-19 pandemic

Kakos CD *et al.* Pediatric transplantation during the COVID-19 pandemic

Abstract

Children infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seem to have a better prognosis than adults. Nevertheless, pediatric solid organ transplantation (SOT) has been significantly affected by the unprecedented coronavirus disease 2019 (COVID-19) pandemic during the pre-, peri-, and post-transplant period. Undoubtedly, immunosuppression constitutes a real challenge for transplant clinicians, as increased immunosuppression may prolong disease recovery, while its decrease can contribute to more severe symptoms. To date, most pediatric SOT recipients infected by SARS-CoV-2 experience mild disease with only scarce reports of life-threatening complications. As a consequence, after an initial drop during the early phase of the pandemic, pediatric SOTs are now performed with the same frequency as during the pre-pandemic period. This review will summarize the currently available evidence regarding pediatric SOT during the COVID-19 pandemic.

Key Words: Pediatric; Transplantation; SARS-CoV-2; COVID-19; Immunosuppression

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Core Tip: Pediatric patients experience milder symptoms of coronavirus disease 2019 (COVID-19). Pediatric solid organ transplantation (SOT) during the COVID-19 pandemic represents a real challenge not only for the SOT candidates and recipients but also for the transplant clinicians. Immunosuppression increases the risk of COVID-19 but may also provide a benefit against possible infection, as it lowers the risk of a catastrophic hyperinflammatory response from the host. We herein review the currently available evidence regarding pediatric SOT during the COVID-19 pandemic.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) had caused an unprecedented impact for all people worldwide and particularly for people with chronic underlying comorbidities. Specifically, people with weakened immunity either due to an underlying disease or due to immunosuppression are at high risk. Although children represent just 2%-10% of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnostic cases and seem to have less severe disease when compared with adults^[1], pediatric solid organ transplantation (SOT) candidates and recipients have been significantly afflicted by the pandemic. The aim of this review is to summarize and discuss the currently available data regarding pediatric SOT during the COVID-19 pandemic.

CHILDREN AND COVID-19

It is well known now that children experience milder disease when compared with adults and a lower proportion of children will require hospitalization^[2,3]. The most frequently reported symptoms are cough and fever, while some pediatric patients may also present with gastrointestinal symptoms^[4]. Although fatalities are rare in the pediatric population, 2%-8% of children with COVID-19 will eventually require admission to an intensive care unit^[5]. Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 is a post-infectious consequence of pediatric SARS-CoV-2 infection presenting with gastrointestinal, cardiac, renal, or neurologic manifestations^[6].

There has been excessive research on why adults experience more severe form of COVID-19. A key concept is the difference between the pediatric and adult immune systems. Except for the most severe SARS-CoV-2 cases, children appear to preserve CD8+ cytotoxic response^[6-8], as they do not face the immunosenescence that normally occurs with aging. Data have also shown that children might have more powerful adaptive immunity^[9], as for example pediatric SARS-CoV-2 patients do not present with either lymphopenia or high neutrophil/lymphocyte ratio^[6]. In addition, adults have higher levels of circulating pro-inflammatory cytokines [interleukin-1 β (IL-1 β), IL-6, IL-10, IL-12, interferon- γ , tumor necrosis factor- α (TNF- α), C-reactive protein] than

pediatric SARS-CoV-2 patients^[10-12], although in a study from New York City, IL-6 and TNF- α values did not differ from adults^[13].

A finding that needs further investigation is the potential role of angiotensin-converting enzyme 2 (ACE2) receptor, which is the main binding protein of SARS-CoV-2 on host cells^[14]. ACE2 has been described as an anti-fibrotic and anti-inflammatory agent against pulmonary leak and inflammation, thus ACE2's higher expression that has been observed in children, may contribute to the fact that children are more resistant to SARS-CoV-2^[7].

Furthermore, the fact that children typically do not have significant comorbidities, such as arterial hypertension, diabetes mellitus, or congestive heart failure, may contribute to the milder cases of COVID-19 observed. Associated factors that predispose to a negative outcome in children with SARS-CoV-2 are not well defined^[15]. Nevertheless, previous studies have identified obesity, hypoxemia at clinical presentation, asthma, congenital heart disease, inherited metabolic syndrome, chromosomal disorders, and ethnicity as risk factors for severe SARS-CoV-2 infection in children^[16-19]. Last but not least, another theory suggests that common childhood infections (respiratory syncytial virus, mycoplasma pneumoniae) can carry out cross protection, so children who have recently recovered from these infections may have higher immunoglobulin G (IgG) titers than adults^[20,21].

SARS-COV-2 AND HEPATIC/RENAL MANIFESTATIONS IN CHILDREN

SARS-CoV-2 enters the liver parenchyma through the ACE2 receptor, however, the liver is only rarely affected seriously by the disease, most probably due to its tolerogenic environment^[22,23]. The most common hepatic manifestation is an elevation of hepatic transaminases in 6%-27% of pediatric cases, a mild elevation of γ -glutamyl transferase, alkaline phosphatase, and total bilirubin, yet its clinical significance remains unclear^[24]. The liver damage may be directly caused by viral infection of the liver cells, from medications like remdesivir or lopinavir/ritonavir, or from chronic hypoxia^[25-27].

High levels of IL-6 and IL-10 are associated with severe SARS-CoV-2 infection, but not with SARS-CoV-2-related with abnormal liver enzymes^[28].

A cohort study from the United States and the United Kingdom demonstrated that adults with chronic liver disease (CLD) and cirrhosis are prone to increased risk of adverse outcomes following SARS-CoV-2^[29]. A study from northern Italy noted that adults and children with autoimmune liver disease maintained satisfactory health status despite their imbalanced immune system^[30]. Another Italian multicenter study which included both cirrhotic and non-cirrhotic liver disease patients demonstrated that 84% of children with CLD remained healthy during the outbreak^[9]. It remains unclear whether children with CLD experience more severe symptoms.

SARS-CoV-2 can also present with renal manifestations, while several studies suggest that kidney transplantation should be continued during the COVID-19 pandemic under certain precautions^[31-34]. ⁹ Acute kidney injury is mostly associated with immune alterations and direct cytopathic lesions by SARS-CoV-2^[35]. Acute tubular injury is also a common yet typically mild manifestation^[36]. Comorbidities, such as diabetes mellitus and cardiovascular disease, can delay recovery from acute kidney injury^[37]. A multicenter study from Turkey revealed that incidence of SARS-CoV-2 is higher in pediatric patients on dialysis or after kidney transplantation, yet the authors admit that regional factors, such as the high population, the crowded households, and socioeconomic status in Istanbul, may have contributed to this particular observation in that cohort^[38]. They also found that hospitalization rate was higher in dialysis patients than among kidney transplantation recipients, potentially due to a higher proportion of asymptomatic disease in kidney transplantation recipients^[38].

IMPACT OF SARS-COV-2 ON PEDIATRIC TRANSPLANTATION

It was inevitable that the COVID-19 pandemic would affect the transplant activity worldwide. A multicenter analysis of the European reference network on pediatric transplantation showed a substantial reduction of pediatric transplants across Europe^[39]. This was related to the precautions and measures to minimize SARS-CoV-2

transmission, the shortage of hospital beds and staff, the restrictions in operation room availability, and a notable decline in the recovery of deceased donor organs, especially during the early phase of the pandemic^[40]. Additionally, United States data from the Scientific Registry of Transplant Recipients showed an initial decrease in pediatric kidney transplants from both deceased and living donors by 47% and 82%^[41]. Subsequently, there was a continual increase with numbers reaching the expected pre-pandemic levels by May 2020^[41]. The authors also reported a 189% increase in waitlist removal due to mortality or deterioration^[41]. Kemme *et al*^[42] used the same registry studying pediatric liver transplantation. They found a decrease in waitlist addition by 25% between March and May of 2020, with black candidates being affected the most. During the early phase of the pandemic there was a 38% reduction in pediatric liver transplantation, with black children experiencing an 81% decline in living donor liver transplantation, in contrast to white children who faced no change in this category. Overall, white children had a 30% drop in liver transplantation during the pandemic^[42]. Figure 1 depicts the number of pediatric kidney and liver transplants performed in the United States between January 1st, 2020, and January 1st, 2022.

PEDIATRIC TRANSPLANTATION DURING THE COVID-19 PANDEMIC

Except for universal recommendations from transplant societies worldwide, there are no mandatory guidelines specific to pediatric SOT during the pandemic. The decision for SOT depends on the urgency of the need for a new organ and the risk-to-benefit ratio. Both pediatric SOT candidates and living donors should follow prevention strategies to reduce potential exposure to SARS-CoV-2 in the pre-transplant period. Self-quarantine for 14 day prior to living donation is important, while a negative swab test for both the candidate and the donor upon admission to the hospital should also be required. Particularly in case of pediatric SOT, the caregiver should also be asymptomatic and have a negative swab test prior to transplant. Further, most transplant societies strongly mandate universal SARS-CoV-2 screening of potential deceased donors before organ procurement^[43].

There is no consensus about the optimal time for a transplant when the potential donor had a SARS-CoV-2 infection. In general, it is recommended to avoid grafts from donors with active SARS-CoV-2 infection^[44], while there are different acceptance criteria for donors who have recently recovered from it^[43]. Some transplant societies recommend using a graft from a living donor at least 28 d after symptom resolution irrespective of real-time polymerase chain reaction (RT-PCR) positivity. Due to the pulmonary and renal dysfunction associated with SARS-CoV-2 infection, additional considerations may be appropriate when the procedure involves transplantation of lungs or kidneys from a previously infected donor.

There is a scarcity of data regarding the optimal time of SOT in case a pediatric candidate is infected by SARS-CoV-2. Ideally, the candidate should be both asymptomatic and have a negative test. Notably, Goss *et al*^[45] reported an uncomplicated liver transplantation in a child positive for SARS-CoV-2 on a nasopharyngeal swab test just 4 wk before transplant. The IgG specific antibodies persisted for 6 wk after liver transplantation, with unaltered immunosuppression per the center's standard protocol^[45]. Until additional data are available, the risk of the procedure must always be weighed against the risk of deferring SOT.

On another note, technology overall has significantly changed the way people communicate during the COVID-19 pandemic, and thus telemedicine can have a pivotal role on transplant follow-up as it facilitates the general rules for social distancing^[46]. However, a German study showed that most young adults who underwent liver transplantation in childhood were afraid to attend medical appointments and 40% reported lower appointment adherence^[47]. Additionally, although video consultations might be helpful for follow-up, their acceptance by liver transplantation recipients was lower than expected^[47]. It is important that pediatric patients adhere to follow-up appointments after SOT but also their parents should notify the transplant provider of any suspected or proven SARS-CoV-2 exposure and discuss whether additional measures are needed. Careful hand hygiene and avoidance of crowds during the period of high immunosuppression are key strategies for prevention of a possible infection^[48].

Finally, several studies have evaluated the SARS-CoV-2 vaccine safety and efficacy in SOT recipients and children, with nearly all of them supporting that the administration of at least two vaccine doses in these patients is safe and efficient^[49-55]. There is also an ongoing study approved by Johns Hopkins University examines the levels of SARS-CoV-2 antibodies in children who are organ transplant candidates or recipients before and after they get the SARS-CoV-2 vaccine (IRB00248540).

MANAGEMENT OF SARS-COV-2 POSITIVE PEDIATRIC TRANSPLANT RECIPIENTS

A confirmed SARS-CoV-2 case requires laboratory evidence of viral detection. The testing strategies vary by geographical location and testing capacity. A nasopharyngeal RT-PCR test is the recommended gold standard. However, a negative RT-PCR test does not definitively exclude SARS-CoV-2 infection and the reported rate of false negative results vary between 2%-29%^[56]. If symptoms persist, a second nasopharyngeal RT-PCR test should be performed after 48-72 h. Depending on the time of the year, an evaluation for other respiratory viruses should be considered. An alternative diagnosis would reduce but not eliminate the possibility of COVID-19, while the detection of another respiratory pathogen may require additional management (*e.g.*, antiviral treatment in case of influenza infection).

Antibody tests should not be used to diagnose acute SARS-CoV-2 infection, while their application to assess the host response after an infection is an area under investigation. It is unknown if pediatric SOT recipients mount a robust serologic response to SARS-CoV-2, and even in case they have protective antibodies, for how long the duration of this protection will last^[53-55]. Single center studies from Saudi Arabia and Brazil have showed a relatively high seroprevalence of SARS-CoV-2 in the pediatric kidney transplantation population^[57,58]. However, there are concerns for possible false positive antibody results due to cross-reactivity with other coronaviruses^[59].

The management of a confirmed case of SARS-CoV-2 positive pediatric SOT recipient is mainly supportive, with supplemental oxygen, non-steroidal anti-inflammatory drugs, remdesivir, dexamethasone, and SARS-CoV-2 convalescent plasma being the only proven measures that can affect significantly the outcome^[26,60,61]. Lopinavir, ritonavir, and hydroxychloroquine have not shown any significant benefit in mortality and morbidity, including the need for mechanical ventilation^[60].

A crucial aspect in this group of patients is immunosuppression, which is generally considered a double-edged sword^[62]. Increased immunosuppression may increase the viral load and delay recovery, whereas low immunosuppression may contribute to severe COVID-19 forms due to a more robust immune response^[63]. In fact, SARS-CoV-2-induced pulmonary injury is mainly driven by excessive activation of host's innate immune inflammatory response^[64]. Despite that notion, it has been proposed that immunosuppression in immunocompromised children may not actually increase the risk for severe SARS-CoV-2 disease^[65]. On the contrary, SOT recipients may benefit from immunosuppressive drugs, as they will dampen the cytokine storm^[66,67]. Immunosuppression has not been reported as strong of a risk factor as obesity, chronic comorbidities, or increased age. One possible explanation is that in SARS-CoV-2, unlike other viral agents (*e.g.*, adenovirus, rhinovirus, norovirus, influenza), the host immune response is the main driver of lung tissue damage during infection^[65]. Interestingly, a systematic review showed that immunosuppressed patients have a lower incidence of SARS-CoV-2 infection when compared with the general population and they may exhibit relatively favorable outcomes as compared to other comorbidities^[68].

The impact of immunosuppression on COVID-19 severity in pediatric SOT recipients remains unclear. Although complete withdrawal of immunosuppression might not be the optimal approach, individual modifications may be necessary in case of moderate-to-severe SARS-CoV-2 infection^[69]. It seems that some immunosuppression may allow for control of the dysregulated immune response, which is commonly observed in severe SARS-CoV-2 infection^[65,69]. Comparative data on immunosuppression management strategies are not yet available. Some authors recommend decreasing or

discontinuing cell cycle inhibitors and cautiously reducing calcineurin inhibitors (*i.e.*, cyclosporine, tacrolimus) in moderate-to-severe COVID-19 in adult SOT recipients, while others recommend continuing calcineurin inhibitors and steroids and stop anti-proliferative medication^[70]. It is also thought that calcineurin inhibitors might exert an antiviral effect¹ and also inhibit IL-6 and IL-10 pathways, which are involved in the immune dysregulation observed in COVID-19 patients^[71]. In addition, certain immunosuppression therapies like mammalian target of rapamycin (mTOR) inhibitors may even have biologic activity against SARS-CoV-2^[72].

Transplant centers follow their own strategies based on their institutional experiences. Although the data for pediatric patients are scarce, Colmenero *et al*^[73] observed no adverse outcome with the use of calcineurin inhibitors and mTOR inhibitors in adult patients. On the other hand, mycophenolate mofetil (MMF) was associated with severe SARS-CoV-2 infection¹ in a dose-dependent manner^[74]. This can be explained by its mechanism of action, as MMF produces a cytostatic effect on activated lymphocytes^[74]. It is well known that SARS-CoV-2 is associated with lymphopenia, so MMF may exert a synergic and deleterious effect on depleting peripheral lymphocytes³. On the contrary, mTOR inhibitors increase the quality and functionality of memory T-cells and reduce the replications of multiple viruses including cytomegalovirus, Epstein-Barr virus (EBV) and human immunodeficiency virus^[75]. Regarding calcineurin inhibitors, some studies have shown *in vitro* antiviral effects against coronaviruses, and also that they can ameliorate the cytokine storm^[76]. Randomized clinical trials comparing the different immunosuppressive schemas would help us guide management of both adult and pediatric SOT recipients.

In case there is strong suspicion for bacterial superinfection, the administration of antibiotics, such as moxifloxacin, levofloxacin, ceftriaxone, vancomycin, or amikacin can be considered^[77-79]. Azithromycin should be used with caution in SOT recipients as it can increase the levels of tacrolimus^[80]. These medications have been prescribed mainly in unresponsive cases, which precludes us from deducing meaningful conclusions in the absence of high-quality data.

OUTCOMES IN SARS-COV-2 POSITIVE PEDIATRIC TRANSPLANT RECIPIENTS

There are several recent reports of pediatric SOT recipients who have been infected by SARS-CoV-2 (Table 1)^[38,57,58,66,77-79,81-98]. For example, Heinz *et al*^[81] reported mild symptoms in a 6-mo-old recipient just 4 d after liver transplantation, while the infection was probably transmitted from the mother-donor. Neither the donor nor the recipient were tested pre-transplant due to low availability of rapid testing at the early phase of the pandemic^[81]. A multicenter study documented no mortality due to COVID-19, but a high rate of acute liver injury in pediatric liver transplantation recipients^[83]. Morand *et al*^[82] reported a co-infection of SARS-CoV-2 and EBV in a pediatric liver transplantation recipient that was managed with slight reduction of tacrolimus. Nikoupour *et al*^[78] reported a fatal outcome in a 3-year-old liver transplantation recipient after multiorgan failure and cardiorespiratory arrest. Results from the same transplant center reported a 100% death rate in 4 pediatric liver transplantation recipients due to liver failure, implying an increased mortality risk in children^[84]. A case report from Texas described a case of multisystem inflammatory syndrome with features of Kawasaki disease in a 3-year-old African American female liver transplantation recipient^[86]. The patient did not require transfer to the intensive care unit and was effectively managed with tacrolimus titration^[85].

There are also some interesting findings in pediatric kidney transplantation recipients. Berteloot *et al*^[86] presented nine pediatric cases, seven of whom developed graft arterial stenosis during early follow-up after kidney transplantation. It was reported as immune post viral graft vasculitis triggered by SARS-CoV-2^[86]. Levenson *et al*^[87] reported acute kidney injury in an adolescent male kidney transplantation recipient following SARS-CoV-2 infection, with biopsy showing segmental glomerulosclerosis on a background of chronic active antibody-mediated rejection. The case was treated with an overall reduction of immunosuppression, along with anti-inflammatory treatment, which proved to be effective in preserving allograft function while attaining recovery^[87]. Finally, a multi-center, multi-organ case series from five

transplant centers across the United States demonstrated favorable outcomes in pediatric SOT recipients⁶ with COVID-19, which may mirror those of immunocompetent children, with infrequent hospitalizations and minimal additional treatment requirements^[66].

CONCLUSION

Pediatric transplantation is a complex process that requires a combination of resources and specialized professionals and has been significantly impacted by the COVID-19 pandemic. Overall, there was a substantial decrease in pediatric transplantation during the early phase of the pandemic, yet recent findings show that pediatric SOT outcomes during the pandemic are favorable. The results on the safety and efficacy on vaccines have been promising, yet further research is required to draw more solid conclusions on the optimal immunosuppressive management of pediatric SOT recipients.

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