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The impact of COVID-19 on the pediatric solid organ transplant population

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly impacted all aspects of healthcare including solid organ transplantation. In this review, we discuss the specific impact of COVID-19 on the pediatric solid organ transplant population including access to grafts for pediatric transplant candidates as well as COVID-19 disease manifestations in pediatric transplant recipients. We address the current knowledge of prevention and management of COVID-19 in pediatric transplant recipients and provide additional information regarding social distancing, infection prevention and return to school.

Introduction on COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral agent causing coronavirus disease 2019 (COVID-19), was identified in late 2019 with a pandemic declared by the World Health Organization in March 2020. Since that time, more than 480 million cases and 6 million deaths have been reported worldwide, impacting every aspect of daily life including solid organ transplant (SOT).[1]

General impact of COVID-19 on solid organ transplant programs

At the start of the pandemic there were significant uncertainties about the mechanisms of COVID-19 transmission and what potential exposure might occur during transplantation for donors, recipients and procurement and transplant staff. Additionally, there were concerns about the ongoing availability of health care resources necessary for transplantation including personal protective equipment, ventilators and hospital beds.[2] These concerns resulted in an acute decrease in transplant volume across the United States. In the early pandemic period (3/15/2020–4/30/2020) there were 11% fewer listings on the liver transplant waitlist, 49% fewer living donor liver transplants, 9% fewer deceased donor liver transplants and 59% more waitlist deaths in states with high COVID-19 incidence compared to what was expected from historical transplant trends.[3] Likewise, during the same time period there were 18% fewer listings on the kidney transplant waitlist, 87% fewer living donor kidney transplants, 24% fewer deceased donor kidney transplants and a 2.2 fold higher incidence of waitlist deaths in states with high COVID-19 incidence compared to what was expected from historical trends.[2] Seventy-two percent of living donor kidney transplant programs and 68% of living donor liver transplant centers completely suspended new transplantation early on in the pandemic.[4] While the impact on pediatric transplantation activity was not quite as significant as the impact on adult transplantation activity, similar trends were observed. Early in the pandemic pediatric living donor kidney transplants were down 82%, pediatric deceased donor kidney transplants were down 47%, pediatric kidney waitlist inactivation rose 152% and pediatric kidney waitlist removal due to death or deteriorating condition rose 189% above expected levels.[5] Likewise, early in the pandemic there was a 38% decrease in pediatric liver transplantation and a 25% decrease in pediatric liver waitlist additions.[6] In late 2020 and 2021, both adult and pediatric transplantation rebounded suggesting adaptability and resiliency of the transplant community.[3,7] However, pediatric SOT volumes remained below pre-pandemic levels (2019: 1908 pediatric SOTs, 2020: 1762 pediatric SOTs; 2021: 1881 pediatric SOTs).[8]

Abbreviations: AST, American Society of Transplantation; COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant.

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COVID-19 infections in pediatric solid organ transplant recipients

When the pandemic began, the transplant community was concerned that infection with COVID-19 would result in severe illness for transplant recipients on immunosuppressive medications as with many other viral illnesses including cytomegalovirus, Epstein Barr virus, herpes zoster virus, varicella zoster virus, adenovirus, norovirus, influenza, BK virus and respiratory syncytial virus.[9–13] However, over the past two years it has become apparent that this is not the case.[14,15] In a multicenter international observational registry including 180 pediatric liver transplant recipients with laboratory confirmed SARS-CoV-2 infection, none of the transplant recipients required mechanical ventilation or died.[15,16] In another multicenter observational registry through the Pediatric Heart Transplant Society Registry, of 866 pediatric heart transplant recipients with COVID-19, only 14% required hospitalization, 5% required intensive care unit (ICU) admission, 1% required ventilation and less than 1% died.[17] Much of the morbidity and mortality associated with COVID-19 is now understood to be due to an exaggerated host immune response as opposed to direct viral cytopathic injury.[7,18] As a result, being on chronic immunosuppressive medications may be protective against severe COVID-19.[14–16,19,20] Calcineurin inhibitors may specifically help to inhibit Coronavirus replication.[21] In a European observational registry including 243 adult liver transplant recipients with laboratory confirmed SARS-CoV-2, tacrolimus use had a positive independent effect on survival (HR, 0.55; 95% CI, 0.31–0.99).[20] Additionally, corticosteroids have been reported to decrease need for invasive ventilation, decrease the length of stay in the ICU and decrease the 28 day mortality among patients receiving ventilatory support or oxygen.[22,23] Anti-metabolites have demonstrated antiviral properties *in vitro*.[24] Therefore, at this time there is no evidence to support reduction or elimination of immunosuppression solely due to COVID-19.[14]

Management of COVID-19 infection in pediatric solid organ transplant recipients

As the pandemic evolved, so too did the understanding and availability of therapeutics directed at COVID-19. During the earliest phase, several agents were trialed, including hydroxychloroquine and azithromycin, that were subsequently discovered to have little impact on the course of disease.[25] Subsequently, phases of care have included supportive care, antiviral therapy (primarily remdesivir), glucocorticoid administration, immunomodulator delivery, and early intervention with convalescent plasma or monoclonal antibody infusions.[26] Recently, a study compared the outcomes of 129 adult SOT recipients with COVID-19 across two COVID-19 therapeutic eras (Era 1: March-May 2020, Era 2: June-November 2020). In Era 1, no patients received remdesivir or dexamethasone and 19% received convalescent plasma; in Era 2 43% received remdesivir, 43% received dexamethasone and 71% received convalescent plasma. There was no observed difference in mortality, hospital length of stay, allograft dysfunction, renal or liver function, or infectious complications between the two different eras of therapeutics.[27]

Early reports in pediatric SOT recipients identified supportive care alone as the primary intervention, with limited numbers of pediatric SOT recipients exhibiting severe or critical disease. Most pediatric SOT cohorts reported hospitalization in 15-25% of patients with only a minority (1–7%) needing ICU-level care and only a handful of deaths attributed to COVID-19.[15,28–33] These cohorts principally included patients identified during the first waves of infection. The more recent Delta and Omicron variants have had greater impact on children. Recommended therapies for these variants have been based on extrapolation from studies in healthy adults. To date the published literature on use of remdesivir, glucocorticoids and monoclonal antibodies for COVID-19 is limited to a case report of two pediatric SOT recipients hospitalized with COVID-19 who recovered after treatment with dexamethasone.[29] Several organizations including the National Institutes of Health have developed evidence-based guidance documents for prevention and treatment of COVID-19.[26] Based on these guidance documents and the reported epidemiology in SOT to date, organizations such as the Society for Pediatric Liver Transplantation and the American Society of Transplantation (AST), have extrapolated therapy recommendations to SOT recipients including the use of antivirals, glucocorticoids and monoclonal antibody preparations as locally available.[14,34] Monoclonal antibodies, given with early symptoms to prevent progression to severe disease requiring hospitalization, have evolved with different preparations providing coverage depending on the circulating COVID-19 variant. For example, both bamlanivimab/etesevimab (Eli Lilly and Company, Indianapolis, IN) and casirivimab/imdevimab (REGEN-COV, Regeneron Pharmaceuticals Inc, Tarrytown, NY) exhibited less activity against the Omicron variants BA.1 and BA.2, and sotrovimab (GlaxoSmithKline LLC, Philadelphia, PA) exhibited reduced activity against Omicron variant BA.2; leading to the current recommendation for use of bebtelovirmab (Eli Lilly and Company, Indianapolis, IN) while BA.2 is circulating.[26,35] Additionally, the AST acknowledges the complexity of using some antiviral therapy, like ritonavir-boosted nirmatrelvir (Paxlovid, Pfizer, New York City, NY), due to significant drug-drug interactions with calcineurin inhibitors and the complexity of monitoring calcineurin inhibitor levels in a patient with active COVID-19 infection.[36] The use of immunomodulatory agents such as IL-6 receptor antagonists (tocilizumab) and JAK inhibitors (barcitinib) have shown promise in adult trials[37–40], but neither pediatric studies nor significant studies in SOT recipients have been reported to date. Interestingly, the impact of convalescent plasma was reported in a cohort of 66 adult SOT recipients who received therapy a mean of 9 days after COVID-19 disease onset.[41] Improvement in oxygen requirement occurred in 68%, and the cohort had only 14% mortality. However, it is less likely that this therapy will be adopted in pediatric SOT recipients who have less morbidity and mortality compared to adult SOT recipients.

Overall, the therapeutic options for combating COVID-19 have been evaluated and reported in adult patients, however; additional data is urgently needed regarding optimal therapy for pediatric patients, including pediatric SOT recipients.

Prevention of COVID-19 in pediatric solid organ transplant candidates and recipients

Immunization

The Pfizer-BioNTech BNT162b2 vaccine, available starting in December 2020 under emergency use authorization, was approved by the Federal Drug Administration for individuals 16 and older in August 2021. Thereafter, the vaccine received emergency use authorization by the Federal Drug Administration for children ages 5 and older.[42–45] The AST currently recommends COVID-19 vaccine for age-eligible solid organ transplant candidates, recipients, living donors and household members and caregivers in order to help prevent infection and reduce severity of clinical disease if acquired. Whenever possible, vaccination should occur at least 2 weeks prior to transplantation. When vaccination against COVID-19 pre-transplant is not possible, COVID-19 vaccine can be administered as early as 1-month post-transplantation. If the child received T- or B cell ablative therapy (i.e. thymoglobulin or rituximab), then waiting 3 months may be more appropriate.[46]

Preliminary data suggests that the serologic response to a two-dose primary COVID-19 vaccine series is dampened in pediatric solid organ transplant recipients. In a study of 52 pediatric solid organ transplant recipients aged 12-18 years who received the

Pfizer-BioNTech BNT162b2 vaccine, 73% demonstrated a positive antibody response after two doses. Shorter time from transplantation, use of multiple immunosuppressive agents, and use of an anti-metabolite agent were associated with a negative antibody response. In this cohort, none of the vaccinated children experienced any serious adverse events including allergic reaction, myocarditis, new neurologic condition, organ rejection or death.[47] Early data suggests an additional immune benefit of a third vaccine dose in pediatric solid organ transplant recipients. In a study of 43 patients who received three BNT162b2 doses, 88% had positive antibodies one month after the third COVID-19 vaccine dose. In this study none of the children experienced any serious adverse events; however, there were four cases of breakthrough COVID-19 infections.[48] To date, there are no published reports of myopericarditis amongst COVID-19 vaccinated SOT recipients.[49] At this time, moderately to severely immunocompromised children ages 5–11 are recommended to complete a primary series of 3 doses of COVID-19 vaccine and children ages 12 and above should receive a primary series of 3 doses of an mRNA COVID-19 vaccine, plus 2 boosters of an mRNA COVID-19 vaccine (4th and 5th dose).[50] We anticipate that in the future a booster doses may also be recommended for younger children and therefore would urge transplant teams to refer to the most up-to-date recommendations from the Centers for Diseases Control and Prevention.[45]

Transplant recipients who are unvaccinated and acquire COVID-19 infection should still get vaccinated after recovery from their infection as protective immunity is generally lower after infection than after vaccination.[51] Unvaccinated transplant recipients can receive vaccine as soon as they have recovered from the virus and no longer require isolation.[49] Parents, guardians and other household members around pediatric solid organ transplant recipients should also be encouraged to get vaccinated. Further studies are needed in larger groups of pediatric solid organ transplant recipients to assess the most immunogenic vaccine formulation, ideal number of vaccine doses, the optimal timing of initial vaccination, need for booster vaccine doses, and durability of immunologic protection.[52] Additionally, data are needed to understand the impact of virus-specific T-cell responses in solid organ transplant recipients with low antibody response.[46]

Pre-Exposure Prophylaxis: Tixagevimab/cilgavimab (Evusheld, AstraZeneca Pharmaceuticals LP, Wilmington, DE) is an intramuscular injection approved for SARS-CoV-2 pre-exposure prophylaxis in children ages 12 and above and weighing more than 40 kilograms who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection and who are either moderately to severely immunocompromised or unable to receive COVID-19 vaccine.[26] Evusheld should not be a substitute for vaccination and is recommended only for those children who did not mount a protective response to vaccine or who have a medical contraindication to vaccine.[46] Data on use in pediatric SOT recipients are extremely limited at this time.

Return to in-person education

Pediatric transplant recipients and their families continue to face decisions about when to return to school and what protective measures to take while at school. Risk of acquiring COVID-19 at school is dependent on a combination of patient, community, and school-related factors.[49] Patient factors include level of immunosuppression, current graft function and potential need for increased immunosuppression, comorbidities (particularly obesity, diabetes mellitus, chronic lung disease, cardiac dysfunction, neurologic disease, or additional immunocompromising condition), vaccination status of the child and their household contacts, and patient's ability to cooperate with physical distancing and other safety precautions while at school.[49] Community factors include level of community transmission, level of community vaccination and robustness of community contact tracing.[49] School related factors include policies for social distancing, cohorting, symptom screening, good ventilation, hand hygiene and mask wearing.[49] Transplant providers and transplant caregivers must engage in shared decision making to determine the safety and timing of return to school for each individual transplant recipient, especially as local community and school related factors fluctuate. Risk of COVID-19 acquisition at school must be balanced against negative impacts on health if a child remains at home. It is well appreciated that there are mental health and behavioral consequences associated with requiring children to do virtual or remote schooling including loss of peer contact, support services and nutritional programs that are provided through the school.[49]

Conclusions and future directions

The COVID-19 pandemic continues to significantly impact the field of pediatric solid organ transplantation. While transplant volumes have rebounded and many transplant candidates and recipients have received COVID-19 vaccine providing them with future protection, there are still many unanswered questions regarding COVID-19 and much work lies ahead for the transplant community. In terms of graft access and availability, questions remain about the use of COVID-19 positive organs- when is it safe to accept a COVID-19 positive organ and are there different strategies that should be employed if a COVID-19 positive organ is used.[53] For candidates on the waitlist, there is much debate around the country about the ethics of implementing a COVID-19 vaccine mandate for solid organ transplant candidates and potential living donors.[54–57] For transplant recipients, future studies are needed to better understand the humoral and cell-mediated response to COVID-19 vaccine, as well as the length of time that clinical protection remains, and the impact of various degrees of immunosuppression.[47] For those recipients who acquired COVID-19 disease, there is much to learn about optimal therapy and the long-term medical sequelae. Finally, across the entire pediatric population there has been a significant rise in mental health challenges during the COVID-19 pandemic.[58,59] We as a pediatric transplant community will need to find ways to evaluate for mental health problems amongst our patients and to provide additional support for our patients and their families who experiencing mental and emotional distress as a result of the pandemic.

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