











SARS-CoV-2 and pediatric solid organ transplantation: Current knowns and unknowns

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Abstract

The COVID-19 pandemic has proven to be a challenge in regard to the clinical presentation, prevention, diagnosis, and management of SARS-CoV-2 infection among children who are candidates for and recipients of SOT. By providing scenarios and frequently asked questions encountered in routine clinical practice, this document provides expert opinion and summarizes the available data regarding the prevention, diagnosis, and management of SARS-CoV-2 infection among pediatric SOT candidates and recipients and highlights ongoing knowledge gaps requiring further study. Currently available data are still lacking in the pediatric SOT population, but data have emerged in both the adult SOT and general pediatric population regarding the approach to COVID-19. The document provides expert opinion regarding prevention, diagnosis, and management of SARS-CoV-2 infection among pediatric SOT candidates and recipients.

KEYWORDS

children, COVID-19, pediatrics, SARS-CoV-2, SOT

1 | INTRODUCTION

Since the onset of the COVID-19 pandemic in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 67 million infections and 1.5 million deaths

globally.¹ Despite mounting published literature on SARS-CoV-2, data are lacking for pediatric SOT recipients. Our aims are to summarize the available data regarding COVID-19 specific to pediatric SOT using clinical scenarios and highlight knowledge gaps requiring further study. When specific pediatric SOT data were n/a, data from

Abbreviations: ACR, acute cellular rejection; AKI, acute kidney injury; AST, American Society of Transplantation; BAL, bronchoalveolar lavage; bx, biopsy; c/w, consistent with; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CPAP, continuous positive pressure; CXR, chest X-ray; Cy, cyclosporine; DSA, donor-specific antibodies; Dx, diagnosis; ELISA, enzyme-linked immunosorbent assay; ERN, European Reference Network; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; IgG, immunoglobulin G; IPTA, International Pediatric Transplant Association; IST, immunosuppressive therapy; ICU, intensive care unit; IVIG, intravenous immunoglobulin; KTx, kidney transplant; LD, living donor; LFT, liver function tests; LiTx, liver transplant; LRT, lower respiratory tract; LRTI, lower respiratory tract infection; MMF, mycophenolate mofetil; N, number; n/a, not available; NAAT, nucleic acid amplification test; NAT, nucleic acid amplification test; NCP, nucleocapsid protein; nd, not documented; NP, nasopharyngeal; NPS, nasopharyngeal swab; NPV, negative predictive value; OHT, orthotopic heart transplant; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PPV, positive predictive value; pred, prednisone; PTD, post-transplant day; RBD, receptor-binding domain; RNA, ribonucleic acid; RT-PCR/NAT, real-time polymerase chain reaction/nucleic acid test; S1, S2, spike protein 1, spike protein 2; SARS-CoV-2, severe acute respiratory coronavirus 2; SOT, solid organ transplantation; SPLIT/TTS and NASPGHAN, Society of Pediatric Liver Transplantation/The Transplantation Society and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; TDM, therapeutic drug monitoring; TTS, The Transplantation Society; URI, upper respiratory infection; URT, upper respiratory tract; US, United States; VL, viral load; y, year.

TABLE 1 Summary of published or publicly available COVID-19 data among pediatric (≤ 21 year) solid organ transplant recipients

Ref	Age (in year)	Graft, N	Manifestation/Time post-SOT/IST at Dx	Labs	Management	Outcome	Comment
[39]	nd	LiTx (3)	No clinical disease	SARS-CoV-2 RT-PCR+	nd	Alive, well	3/200 LiTx+: Low incidence of COVID-19 in SOT in Bergamo, Italy
[40,42]	0.5	LiTx, LD (1)	<ul style="list-style-type: none"> Day 4 post-transplant, steroid induction Fever, respiratory distress, diarrhea 	<ul style="list-style-type: none"> PTD 2 + SARS-CoV-2 RT-PCR in donor (mother) and child (nasal); RT-PCR not performed on blood or liver tissue PTD 6: 5x increase in LFTs and CXR with patchy lung opacities PTD 7: liver bx with moderate acute hepatitis, mixed portal inflammation (lymphocyte predominant) in most portal tracts with lymphocytic cholangitis and mild portal venulitis, c/w mild-to-moderate ACR (Baniff 5) 	<ul style="list-style-type: none"> Hospitalized: PICU, requiring CPAP PTD 4: hydroxychloroquine (x5 days) and IVIG Treatment of ACR worsened LFTs; corticosteroid tapered and discontinuation of MMF improved enzymes 	Alive, remains hospitalized	Raised question of hepatitis from liver of LD-derived SARS-CoV2
[156]	nd	LiTx (1)	<ul style="list-style-type: none"> URI CNI, pred, tacrolimus 	Not reported	nd	Alive, well	1/190 LiTx+: Low incidence of disease in Sao Paolo, Brazil
[44]	3	OHT (1),	<ul style="list-style-type: none"> 2 y post-OHT Rhinorrhea, productive cough Tacrolimus monotox 	<ul style="list-style-type: none"> SARS-CoV-2 RT-PCR+ (nasal) De novo Class II DSA 	<ul style="list-style-type: none"> No antivirals IVIG (0.5 g/kg) 	Alive	Raised question of SARS-CoV-2 causing de novo DSA
[157]	0.1–17	KTx (3)	<ul style="list-style-type: none"> 1.5–10 y post-KTx Sxs not described Differing: MMF, tacrolimus, everolimus 	<ul style="list-style-type: none"> 2/3 hospitalized and had AKI; 1/3 tacrolimus toxicity IST: MMF reduced/stopped and tacro stopped (1) Unclear if antiviral provided 	<ul style="list-style-type: none"> Alive, recovered; Return to baseline GFR 		
[158]	1.1–15	OHT (3)	<ul style="list-style-type: none"> 0.4–2 y post-OHT Fever, cough, URI, LRT (wheezing), pallor, rash Combination IST (MMF/Cy/pred; tacro/MMF; tacro/azathioprine) 	<ul style="list-style-type: none"> N = 1. hepatitis (SARS-CoV-2 RT-PCRneg) Patient with rash (Gianotti Crosti with negative PCR, positive SARS-CoV-2 IgG ELISA) 	MMF stopped (1)	Alive, recovered	
[41]	13	KTx (1)	<ul style="list-style-type: none"> Fever, cough, diarrhea, hypoxemia 6 y post-KTx Sirolimus, MMF 	<ul style="list-style-type: none"> SARS-CoV-2 RT-PCR+ (NP) ESR 7 mm/hr, CRP 4.5 mg/dL Elevated creatinine 	<ul style="list-style-type: none"> Hospitalized: Supplemental oxygen No antivirals Slight reduction IST (MMF and sirolimus TDM 7 ng/mL) 	Alive, diarrhea persisted x 4 weeks	SARS-CoV-2 RT-PCR+ (NP) at day 28

(Continues)

TABLE 1 (Continued)

Ref	Age (in year)	Graft, N	Manifestation/Time post-SOT/IST at Dx	Labs	Management	Outcome	Comment
[159]	n/a	N = 2 SOT (1 LiTx, 1 NOS); n/a	n/a	Donor was found to be SARS-CoV-2 + post-LiTx	Hospitalized, no further details	n/a	
Dr: Cecil Levy, personal communication (07/06/2020). Nelson Mandela Children's Hospital, Johannesburg, South Africa	13	KTx (1)	<ul style="list-style-type: none"> Rash (pruritic, pustular) Tacrolimus/MMF/ pred 	<ul style="list-style-type: none"> SARS-CoV-2 RT-PCR+ (NP) CRP<10 mg/L Mild AKI 	<ul style="list-style-type: none"> Hospitalized No antivirals No change in IST 	Alive, recovered; return to baseline creatinine	
[160]	11y, 14 y	KTx, 1; LiTx, 1	<ul style="list-style-type: none"> Fever, cough KTx: pred/tacro; LiTx: pred/tacro/MMF 	LRTI infiltrates	<ul style="list-style-type: none"> Both hospitalized No antivirals; hydroxychloroquine in KTx Modifications in IST: KTx 50% tacro reduction; LiTx tacro decrease, MMF withdrawal, pred increase 	No complications, Discharged from hospital (after 2 and 3 days)	
[43]	4.5y	LiTx (1, LD)	<ul style="list-style-type: none"> Fever, cough, rhinorrhea, 5 months post-LiTx Tacrolimus 	<ul style="list-style-type: none"> LRTI focal infiltrate Transaminitis and hyperbilirubinemia Concurrent EBV DNAemia 	No antivirals Tacrolimus reduced 50%	No complications	
[45]	Median 8y	26 total: OHT (6), KTx (8), LiTx (10), Lung (2)	<ul style="list-style-type: none"> Cough (46%), fever (35%), sore throat (12%), rhinorrhea (12%), anosmia (8%), diarrhea (8%) 3.4 years (12–6574 days) post-Tx Varied IST, most frequently tacrolimus-based 	<ul style="list-style-type: none"> 6 (23%) were asymptomatic 5 (19%) required hospitalization for COVID-19-related symptoms for a median of 3 days 8/26 (31%) underwent imaging with 2 demonstrating multifocal LRTI infiltrates 	<ul style="list-style-type: none"> No patient required supplemental oxygen, mechanical ventilation, or ECMO for COVID-19 related symptoms Immunosuppression was reduced in 2/26 (8%) patients, one of whom developed ACR 	No deaths; symptomatic patients recovered within a median of 7 days One patient tested and demonstrated IgG-specific antibody detection	Multi-organ cohort among 5 centers

(Continues)

TABLE 1 (Continued)

Registries				
Ref	Registry	SOT recipients	Publicly available details	Outcome
[161]	Pediatric COVID-19 US Registry	<ul style="list-style-type: none"> N = 90 KTx, 26; OHT, 15; LiTx, 18; Lung, 1; Small bowel, 1 	<ul style="list-style-type: none"> median age: 13y 68/73 had +RT-PCR testing Time of diagnosis: 8 pre-OHT, 65 post-OHT Among 62 patients with completed information: Pre-OHT diagnosis: 71% hospitalized, 43% PICU admission, 14% required mechanical ventilation Post-OHT diagnosis: 31% hospitalized, 13% PICU admission, 4% required mechanical ventilation 	n/a
[162]	Pediatric Heart Transplant Society	N = 73, OHT; N = 65 post-OHT	<ul style="list-style-type: none"> Median age 11.5 y (53% females), presenting most frequently with constitutional or respiratory symptoms 12 hospitalized, 4 in PICU, no mechanical ventilation SARS-CoV-2 therapies in 5: Hydroxychloroquine (2), azithromycin (1), favipiravir (1), IVIG (1) 	<ul style="list-style-type: none"> 54/62 patients with resolution 2 deaths Others unresolved at day 30 or unknown
[163]	SPLIT-TTS and NASPGHAN	<ul style="list-style-type: none"> N = 40, LiTx Distinct IST: tacrolimus, pred, MMF, and/or sirolimus 	Mild symptoms	<ul style="list-style-type: none"> ~50% no change to IST 37 recovered, others still active or pending information No deaths reported
[20]	ERN Transplant-Child	<ul style="list-style-type: none"> N = 40 KiTx, 2; LiTx, 5 		No deaths reported

adult SOT or non-immunocompromised children were provided for additional context.

2 | MATERIALS AND METHODS

Members of the IPTA Infectious Disease Committee, consisting of pediatric infectious disease physicians and nephrologists with expertise in SOT, were convened to review relevant and frequently encountered clinical questions submitted by SOT groups and families related to SARS-CoV-2 and COVID-19 in the pediatric SOT population. Two collaborators reviewed and grouped the questions under distinct content categories that were then used to create the clinical scenarios. Each scenario was then assigned to subgroups consisting of two collaborators who performed a non-systematic review of the available literature to provide data for each scenario response. Each scenario response was then vetted by two other collaborators for internal review and, once approved, sent to the entire group for consensus review. A Delphi technique was used where scenarios and summary statements required approval by all panel members to be included in the final manuscript.

3 | CLINICAL SCENARIOS

3.1 | Case scenario 1: COVID-19 presentation and severity in SOT

A 13-year-old girl, who is now 6 months post-lung transplantation, presents with runny nose without systemic symptoms. The nasopharyngeal swab (NPS) detects SARS-CoV-2 by PCR. She wants to know if she is at increased risk for severe COVID-19 because of her transplant.

Based on emerging data,²⁻⁸ the CDC has included SOT as a risk factor for severe COVID-19.⁹ This is in line with the increased disease severity seen with other viral respiratory infections in this population,¹⁰ particularly influenza.^{11,12} In adult SOT recipients, the clinical presentation of COVID-19 does not seem to differ from that of the general population, with fever and cough being most frequently reported.^{3-5,13} It is unclear whether it is the transplant and ongoing immunosuppression, the associated comorbidities such as diabetes and hypertension, or a combination of factors that place adult SOT recipients at increased risk for severe SARS-CoV-2 infection.^{3-5,13} Clinicians should be aware of the risk for clinical decompensation around day 7–9 of illness. Among adult SOT cohorts, the reported risk of progression to severe disease varies, with need for intensive care and mechanical ventilation occurring in 15%–39% of patients,^{4,14,15} leading to a 20% mortality (range 7%–28%),^{3-6,13} the higher rates seen among SOT recipients with respiratory failure^{3,13,16-20} Disease severity may also depend on graft type, with adult lung transplant recipients presenting with more severe disease whereas KTx recipients had similar disease severity and survival to matched, non-SOT patients with similar comorbidities.^{21,22}

Overall, children are underrepresented among SARS-CoV-2-infected patients, accounting for 2%–10% of diagnosed cases.²³⁻²⁶ The cause of this remains unclear; it is debated whether this is related to a lower attack rate among children^{27,28} or to children presenting more frequently with asymptomatic or mild clinical manifestations, and accordingly being tested less often. Like adults, cough and fever are the most frequently reported symptoms²³; however, 20% of children may also present with gastrointestinal symptoms.²³ Overall, up to 95% of pediatric cases have mild, or moderate symptoms,²⁹ or are asymptomatic, with rates of asymptomatic infection of 20%–30%.^{30,31} Two to eight percent of reported pediatric cases have required admission to the ICU,²⁹ and few deaths have been reported.^{29,32,33} A rare, but potentially severe clinical manifestation of prior COVID-19 in children is the multisystem inflammatory syndrome^{34,35} (also known as pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 [PIMS-TS])^{35,36}. At present, MIS-C is thought to be a post-infectious sequela of pediatric SARS-CoV-2 infection. To date, there are no reported cases of MIS-C after pediatric SOT.

In children, comorbidities are less clearly associated with COVID-19 severity, and therefore, high-risk groups are not well defined.³⁷ Among pediatric patients for which underlying comorbidities were known, obesity is a comorbidity associated with more severe disease, as is hypoxemia at clinical presentation.³⁸ The presence of immunosuppression has been described in up to 12% of patients with COVID-19, although what impact if any, immunosuppression may have on COVID-19 disease severity in the pediatric SOT recipient is unclear.^{23,29} The existing literature regarding COVID-19 in pediatric SOT recipients is limited to case reports and open pediatric registries (Table 1). The few published reports do not highlight an increased severity among SARS-CoV-2-infected SOT children, with most patients presenting with mild or moderate disease, similar to their non-SOT counterparts.³⁹⁻⁴⁶

Viral respiratory infections have been associated with alloimmune responses and potential graft rejection.¹⁰ One pediatric heart transplant recipient has been reported with de novo DSA soon after being diagnosed with SARS-CoV-2 infection, raising the possibility that SARS-CoV-2 infection could be associated with alloimmune responses. However, additional data are needed to elucidate whether SARS-CoV-2 infection may increase the risk for acute graft rejection, either directly or indirectly.⁴⁴

Scenario 1 summary statement: Unlike SARS-CoV-2-infected adult SOT recipients, there are insufficient data to suggest increased SARS-CoV-2 severity in pediatric SOT recipients at this time. Additional data are needed to refute this finding or if confirmed, to understand whether the severity is due to immunosuppression, existing comorbidities, or other factors.

3.2 | Case Scenario 2: Diagnostic considerations

A 3-year-old girl, 6 months post-liver transplantation, presents to the emergency department with fever and cough. Her mother has been

recently diagnosed with COVID-19. A NPS is negative for SARS-CoV-2 by PCR. Parents wonder about the accuracy of the test and the role of antibody tests for the diagnosis of COVID-19.

This clinical scenario highlights the importance of SARS-CoV-2 viral dynamics and rapidly evolving diagnostic testing during the COVID-19 pandemic. A confirmed case of COVID-19 requires laboratory evidence of SARS-CoV-2 detection. The case definition for COVID-19 based on clinical, laboratory, and epidemiological criteria is detailed in Table 2. Testing strategies may vary by geographic location and testing capacity, which may lead to prioritization of diagnostic tests.^{47,48} NAAT and serological (antibody) assays are the testing modalities most frequently used, though antigen-based tests are becoming more widely available. Molecular tests using SARS-CoV-2 NAAT are the reference standard for the diagnosis of acute COVID-19. A real-time RT-PCR assay is recommended for all symptomatic persons with suspected COVID-19.⁴⁷ SARS-CoV-2 RT-PCR testing is also recommended by some experts for asymptomatic individuals with known or suspected exposure to SARS-CoV and in asymptomatic individuals as part of immediate peri-transplant screening in both potential candidates and donors (see scenario 6).^{49,50}

The reliability of SARS-CoV-2 diagnostic tests depends on multiple factors in both the host and assay,^{51,52} with no one test being 100% sensitive or specific. Patient-specific factors including timing from onset of infection, clinical manifestations, compartment

being tested (NP, LRT, stool), and disease severity affect results.^{53,54} SARS-CoV-2 RNA can be detected at high VL in the URT of persons approximately 2 days before symptom onset, generally peaks in the first week of symptoms, and can be detected for a median of 20 days [range 18–55], with duration of detection varying by the compartment being tested and disease severity.^{54–56} In general, symptomatic children tend to have higher initial NP VL when compared with asymptomatic children, with possibly higher VL in severe presentations.^{53,57} Data show that children have similar VL compared with adults.^{58,59} Duration of viral detection in children infected with SARS-CoV-2 occurred for a mean (standard deviation) of 17.6 days (6.7) and median of 19.5 days, becoming undetectable by day 25, and was not dependent on the presence or absence of symptoms, but age may play a role.^{60,61} Not surprisingly, SARS-CoV-2 may be detectable by RT-PCR for a prolonged time in immunocompromised hosts, with detection reported up to 63 days after symptom onset in KTx recipients.^{62,63} However, it is important to note that detection of virus by RT-PCR does not always result in culturable virus.^{54,64–67} Whether the viral tempo and dynamics in immunocompromised children is similar to that reported in adults and immunocompetent children remains to be elucidated.

Other factors affecting reliability of the RT-PCR test result include quality of the sample collected and variables related to assay methodology.⁶⁸ The RT-PCR platform used for SARS-CoV-2

TABLE 2 Case definitions of COVID-19

Criteria	US CDC [164]	EU European Centre for Disease Prevention and Control [165]
Clinical	<ul style="list-style-type: none"> At least <u>two</u> of the following symptoms: <ol style="list-style-type: none"> Fever Chills Rigors Myalgia Headache Sore throat New olfactory or taste disturbances <p>OR</p> <ul style="list-style-type: none"> Severe respiratory illness with at least one of the following: <ol style="list-style-type: none"> Clinical or radiographic evidence of pneumonia Acute respiratory distress syndrome <p>AND</p> <ol style="list-style-type: none"> No alternative diagnosis likely 	<ul style="list-style-type: none"> At least <u>one</u> of the following symptoms: <ol style="list-style-type: none"> Cough Fever Shortness of breath Sudden onset of anosmia, ageusia, or dysgeusia
Laboratory	<p>Confirmatory evidence:</p> <ul style="list-style-type: none"> Detection of SARS-CoV-2 RNA in a clinical specimen using NAT <p>Presumptive evidence:</p> <ul style="list-style-type: none"> Detection of SARS-CoV-2 antigen in a clinical specimen Detection of SARS-CoV-2 antibody in a clinical specimen 	<ul style="list-style-type: none"> Detection of SARS-CoV-2 RNA in a clinical specimen using NAT Radiologic evidence showing lesions compatible with COVID-19
Epidemiologic	<p>One or more of the following exposures in the 14 days before onset of symptoms</p> <ul style="list-style-type: none"> Close contact with a confirmed or probable case of COVID-19 <p>OR</p> <ul style="list-style-type: none"> Close contact with a person with: <ol style="list-style-type: none"> A clinically compatible illness AND Epidemiologic link to a confirmed case of COVID-19 Travel to or residence in a geographic area with sustained SARS-CoV-2 transmission Member of a risk cohort, as defined by public health authorities 	<p>At least one of the following:</p> <ul style="list-style-type: none"> Close contact with a confirmed COVID-19 case in the 14 days prior to symptom onset Being a resident or staff in the 14 days prior to onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed

detection may vary in regard to how many and which RNA genes (nucleocapsid, N; envelope, E; spike, S; RNA-dependent RNA polymerase) are targeted in a single assay. The analytic sensitivity and specificity of RT-PCR are variable by specimen source: 92%–100% and 99%–100%, respectively, from a NP source, 93%–100% and 99%–100% from mid-turbinate, and 59%–94% and 99%–100% from a nasal swab (assuming a pre-test-probability of 10%).^{47,67} Importantly, the true clinical test performance characteristics have yet to be determined and compared across assays.⁶⁸ Lack of a reference standard and suboptimal systematic analysis contribute to reported sensitivities as low as 55%–70%.⁶⁹ Lastly, the diagnostic accuracy of any test result will vary according to pre-test probability and disease prevalence. With increased SARS-CoV-2 prevalence in a community, the PPV of the test increases, while the NPV decreases. All these variables provide the needed context to interpret results of diagnostic testing. Point-of-care technologies (both PCR and antigen-based) are rapidly emerging, but data on performance characteristics are lacking in children and immunocompromised hosts and concerns for test accuracy have emerged. In general, rapid SARS-CoV-2 antigen tests have good specificity, but may have lower sensitivity than PCR-based assays, thus when there is a high suspicion of COVID-19, a standard RT-PCR test should be used.^{47,70}

Antibody tests should not be used to diagnose acute COVID-19, but their application to assess the host response to prior SARS-CoV-2 infection is an area of open study. Multiple antibody tests with varying analytical sensitivity and specificity are available and remain clinically unverified.⁷¹ They have been used for epidemiologic seroprevalence studies or to identify potential candidates for COVID-19 convalescent plasma donation. In some pediatric settings, SARS-CoV-2 serologies have been used to verify a prior diagnosis of COVID-19 in patients who present later during their disease course, including children presenting with MIS-C. Antibody testing has been performed as part of epidemiologic studies in children demonstrate that immunocompromised children, including SOT recipients, have similar seroprevalence than immunocompetent children.⁷² Importantly, it is hypothesized but remains unvalidated whether detection of SARS-CoV-2 antibody correlates with protection and if so, what neutralizing antibody amount and duration is needed to confer protective immunity in both adults and children.⁷³

Similarly to RT-PCR-based assays, the reliability of antibody test results will vary depending on methodologies including limits of detection, immunoglobulin class detected (total antibody, IgM, IgG, IgA, or combined results), the viral antigen targeted (NCP, spike protein [S1 or S2], or RBD), methodology (lateral flow assays, ELISA, or chemiluminescent immunoassays), and whether results are quantitative or qualitative. Timing of testing from symptom onset and disease severity may also affect results.⁷⁴ Among hospitalized adults with COVID-19 of varying severities, antibodies were detected within 10 days after symptom onset, with most patients having evidence of seroconversion by 14–21 days; though sensitivity and specificity varied between commercial assays, antibody concentrations demonstrated correlation with neutralizing antibody

titer.^{73,75,76} Data regarding serologies in SOT recipients are limited to case reports; one case series of seven hospitalized adult SOT recipients who underwent serial antibody testing and all patients developed SARS-CoV-2 IgG (Abbot immunoassay, FDA EUA) a median of 15 days [range 6–27 days] after symptom onset.^{16,62} However, other transplant centers report high false negatives among SOT recipients, who may not mount a robust antibody response.^{77,78} It is unknown whether pediatric SOT recipients will mount a robust serologic response to SARS-CoV-2.^{72,79} If protective, the duration of protection is also unknown.⁸⁰

Lastly, concerns for possible false-positive antibody results secondary to cross-reactivity with other coronavirus have also been reported in some, but not all studies.⁸¹ As 43%–75% of children as young as 6 months to 3.5 years of age have antibodies against one of the four endemic human coronaviruses, this has important implications for possible false-positive results.⁸² Again, clinical performance characteristics of antibody tests will depend on disease prevalence; it is estimated that currently authorized antibody tests with 96%–98% specificity would result in more false-positive than true-positive results if local SARS-CoV-2 prevalence is $\leq 5\%$.⁸³ These knowledge gaps in diagnostic testing have several practical implications, and additional data are needed in both adult and pediatric SOT recipients as we do not know if SOT recipients have higher VL, prolonged viral shedding, and impaired antibody response.

In this case scenario, a SARS-CoV-2 RT-PCR is the appropriate test to be performed, and if the sampling technique was adequate and local SARS-CoV-2 prevalence is $>10\%$, the pre-test probability for possible COVID-19 in this patient is high. However, one negative RT-PCR result does not definitively preclude COVID-19 and reported rates of false-negative results vary between 2% and 29%.⁶⁹ If symptoms persist, repeat NP RT-PCR testing would be indicated 48–72 h later. In cases of LRT symptoms requiring mechanical ventilation, then RT-PCR testing of a LRT specimen is warranted.

Lastly, evaluation for other respiratory viruses, depending on the time of year, should also be undertaken. An alternative diagnosis to explain the child's fever and cough would reduce, but not completely eliminate the possibility of COVID-19. Among patients tested for COVID-19 and other community respiratory viruses, 22% of 49 RT-PCR-confirmed COVID-19 cases and 8.7% of 127 persons with other respiratory viruses were co-infected, most frequently with rhinovirus.⁸⁴ In a case series of pediatric patients hospitalized with RT-PCR-confirmed COVID-19, 19 of 34 (56%) patients underwent additional respiratory testing and had detection of other pathogens, including influenza A, respiratory syncytial virus (RSV), and *Mycoplasma pneumoniae*.⁸⁵ The detection of another respiratory pathogen may require additional management (eg, antiviral therapy if influenza is detected).

Scenario 2 summary statement: A SARS-CoV-2 RT-PCR is the appropriate test to diagnose acute COVID-19, understanding that analytical and clinical performance characteristics of the test may vary based on host factors, timing of infection, and anatomical site tested. Serologic testing should not be used to diagnosis acute

COVID-19; further data are needed to assess their optimal utility in pediatric SOT recipients.

3.3 | Case scenario 3: COVID-19 management

A 9-year-old liver transplant recipient is hospitalized with COVID-19 lower respiratory tract infection (LRTI) and hypoxemia. After 24 h of supplemental oxygen therapy, his respiratory status worsens, and he will likely require intubation and mechanical ventilation. What are potential management options to consider?

COVID-19 severity is categorized into asymptomatic, mild, moderate, severe, and critical.^{86,87} Evidence-based guidelines for the management of suspected or confirmed cases are available,⁸⁶⁻⁸⁹ but the data on which they are based are sparse. Management is therefore mainly supportive. In more severe disease, non-invasive respiratory support or mechanical ventilation may be needed to ensure adequate oxygenation. Need for extracorporeal membrane oxygenation (ECMO) has been described in patients with severe and refractory COVID-19, leading to a reported in-hospital mortality of 15%–39%.^{90,91} Data regarding ECMO support in children are less well categorized and limited to case reports where it was used in both acute COVID-19 and severe MIS-C.⁹²⁻⁹⁶

As the optimal treatment of COVID-19 is an area of emerging study and data in children are lacking, participation in a clinical trial is strongly encouraged. The antiviral remdesivir was granted FDA EUA in the US for the treatment of children hospitalized with COVID-19 weighing at least 8 pounds (3.5 kg) on October 22, 2020.⁹⁷ Preliminary data report that remdesivir shortens the time to clinical recovery in adults hospitalized with COVID-19 pneumonia, but demonstrated no difference in SARS-CoV-2 viral clearance.^{98,99} Other trials do not report clear improvement in patient-specific clinical outcomes, including survival benefit, and thus, societal recommendations regarding its use are heterogeneous.^{89,98,100-102} Dexamethasone has been shown to improve both mortality at day 28 and need for mechanical ventilation among hospitalized patients with COVID-19 who require oxygen supplementation.^{98,103} Lopinavir/ritonavir and hydroxychloroquine have not shown any significant benefit in reducing SARS-CoV-2-related mortality or morbidity, including the need for mechanical ventilation.⁹⁸ The use of adjunctive therapeutics such as immunomodulating agents (tocilizumab, anti-IL1 agents, and interferon beta-1a), or IVIG is considered experimental¹⁰⁴ and could have potential side effects and drug-drug interactions that may be significant in SOT recipients.¹⁰⁵ COVID-19 convalescent plasma given as part of an open-label, expanded access program among hospitalized patients with COVID-19 has been shown to be safe and may be efficacious at high IgG doses if given early, but requires controlled trials that may prove challenging to perform.¹⁰⁶⁻¹⁰⁸ Lastly, monoclonal antibodies have received EUA from the FDA for the treatment of COVID-19 in non-hospitalized patients ≥ 12 years of age (and ≥ 40 kg) with mild- to-moderate symptoms and who are at increased risk for developing severe COVID-19 symptoms or need for hospitalization.¹⁰⁹ Similarly, the FDA issued an EUA for the use

of baricitinib in combination with remdesivir, for the treatment of COVID-19 in hospitalized patients ≥ 2 years of age.^{110,111} The safety and effectiveness of these biologics for the treatment and prevention of COVID-19 require ongoing study, particularly in children.

The optimal approach regarding the management of transplant-related immunosuppressive medications in SOT patients with COVID-19 is also not well defined. Immunosuppressive medications should not be completely withdrawn, though individual modifications are likely needed in cases of moderate-to-severe COVID-19. Currently, it seems that some immunosuppression may allow for control of the dysregulated immune response seen in severe COVID-19.^{39,112} Changes in immunosuppression will depend on COVID-19 severity and timing, type of graft, and time post-SOT, weighing potential risk for acute rejection with possibly prolonging viral shedding leading to poor outcomes. Data regarding the possible effects of SARS-CoV-2 and modifications of immunosuppression on episodes of rejection and graft survival are needed. Comparative data on immunosuppression management strategies are not yet available; some experts recommend decreasing or discontinuing cell cycle inhibitors and cautiously reducing calcineurin inhibitors in the setting of moderate-to-severe COVID-19 in adult SOT recipients. Interestingly, experimental data suggest that certain immunosuppressive therapies may have biologic activity against SARS-CoV-2, for example mTOR inhibitors.¹¹³ In addition, frequently employed calcineurin inhibitors might exert an antiviral effect against SARS-CoV-2^{114,115} and also inhibit IL-6 and IL-1 pathways which are involved in the immune dysregulation seen in severe COVID-19.¹¹⁶ The management of other medications, including ACE inhibitors and ARBs, is also an area of open study with no conclusive data in pediatrics to recommend discontinuation of these medications at this time.

Scenario 3 summary statement: Data regarding the optimal therapy for COVID-19 in the SOT population are lacking. Randomized studies have shown that systemic corticosteroids reduce mortality and the need for mechanical ventilation in patients with severe COVID-19. Data regarding other therapies, including antiviral and antibody-based treatments, are emerging but remain investigational. Reduction of immunosuppression may be considered and individualized for SOT recipients hospitalized with moderate-to-severe COVID-19.

3.4 | Case scenario 4: SOT recipient or their household contacts exposed to SARS-CoV-2

The father of a 9-year-old boy recipient of a liver transplant has been exposed to SARS-CoV-2 at work and asks what can he do to protect his son (A)? Afterward, the father develops symptoms and is ultimately diagnosed with SARS-CoV-2 infection. His son meets exposure criteria, what should be done at this time (B)?

Person-to-person transmission of the virus is most likely to occur if the child is in close proximity (<6 feet per CDC¹¹⁷ or <1 m per the World Health Organization [WHO]¹¹⁸) for ≥ 15 min within 48 h of or after symptom onset in the index COVID-19

case. The major route of spread remains direct contact with secretions of an infected person, particularly if the person is symptomatic. Transmission of SARS-CoV-2 within households has been documented; the absolute risk is estimated to be between 10% and 30%^{27,28,119-122}; with children being less likely to be the index case and preschool children having the lowest likelihood of transmission.^{28,120}

3.4.1 | Potential exposure to SARS-CoV-2

In this scenario, identification of the parent's exposure should be sought to appreciate the potential risk to the patient. The risk is increased if the individual had face-to-face contact without the use of facemasks and eye protection, especially if the primary case is symptomatic. If the father has been exposed, he can immediately take steps to decrease the risk of SARS-CoV-2 transmission to his child and other household members. The father should ideally self-quarantine for 10–14 days after exposure to the confirmed case, that means staying home but maintaining physical distancing from other household members during this period. As isolation policies may vary geographically, clinicians are encouraged to partner with their local public health authorities to have access to the most up-to-date recommendations. If possible, the father should limit his use of shared living spaces, ideally by staying in a separate room with a designated bathroom. Other family members should not share that bathroom when possible, nor towels, cloths, toothbrushes, razors, utensils, food, or beverages. Self-monitoring for symptoms during the incubation period with periodic temperature checks is suggested.¹¹⁷ Masking in the home should be implemented, particularly if appropriate physical distancing cannot be accomplished along with the standard hand hygiene by all family members. A negative RT-PCR result does not modify the quarantine recommendations or infection prevention precautions, nor does it eliminate the possibility of future infection until the incubation period (2–14 days) has elapsed.

3.4.2 | Pediatric SOT recipient with known household contact with proven SARS-CoV-2 infection

SARS-CoV-2 RT-PCR testing is indicated when the father develops symptoms after exposure. The family should re-double efforts to avoid exposure to the infected individual, especially if these were not previously performed. The exposed household contacts should also self-quarantine and perform temperature checks and symptom monitoring as described above. Maintaining physical distancing among all household contacts should be attempted for the initial 10–14 days, although this may be difficult if caring for younger children. The parents should notify the transplant center of any suspected or proven COVID-19 exposures and discuss whether additional measures are needed. The family should not modify any transplant medications without the guidance of the transplant providers as this may increase the risk for adverse events without

affecting the risk of COVID-19 transmission. If the SOT recipient develops symptoms of COVID-19, even if mild, the family should again contact the transplant team for additional recommendations regarding testing and management.

Scenario 4 summary statement: The use of face masks, physical distancing, and hand hygiene are fundamental in preventing exposure to SARS-CoV-2 and subsequent infection. In cases of SARS-CoV-2 exposure, the exposed person should self-quarantine as much as possible, away from other household members, for 14 days. If the exposed person is ultimately diagnosed with SARS-CoV-2 infection, then preventive measures should be further enforced, and other household members should apply self-quarantine measures. All exposures and potential COVID-19 symptoms should be discussed with the SOT recipient's transplant provider.

3.5 | Case scenario 5: Safe living and infection prevention

There is a COVID-19 outbreak in the city, with many cases in the community. The parents of an 11-year-old girl who has received a heart transplantation 1 year ago wonder what they can do to protect their daughter and if she should return to school?

Definitive data-driven safe-living strategies in children after SOT are lacking, but the information presented herein provides some general considerations and guidance. Safe-living strategies in SOT patients and otherwise healthy children are quite similar during the COVID-19 pandemic; some of the practices that parents of healthy children are being asked to enforce are already incorporated into the general recommendations that pediatric SOT patients have used for years. Careful hand hygiene, avoidance of crowds during periods of high immunosuppression, and even wearing a mask during respiratory viral season are not novel strategies to SOT recipients¹²³ and remain integral in mitigating the risk of person-to-person SARS-CoV-2 transmission.¹²⁴

The institution of strict isolation orders in response to the COVID-19 pandemic to slow the spread of infection to a manageable rate is crucial.¹²⁵ However, school plays a critical role in a child's development and well-being. The confinement at home may have profound social, economic, and health consequences with negative effects on children's mental and physical well-being.^{126,127} Students are likely to suffer educational loss during school closure and distance learning has limitations. Some children rely on school meals as their major source of nutrition. In addition, schools provide mental health and other services including occupational health, physical and speech therapies, and a day-to-day structure that have a tremendous positive impact in children's lives. As SARS-CoV-2 epidemiology has changed worldwide, many places have begun to (re)open schools. The decision to reopen schools partially or fully depends on various factors: the local epidemiology of the virus, the school's ability to limit spread of infection, and testing capacity in a particular geographic area. The WHO, UNESCO, and the CDC have offered risk-based approaches and checklists for considering schools reopening.¹²⁸⁻¹³⁰

As schools reopen, whether SOT recipient children should return to school or continue distance learning at home should be assessed on a case-by-case basis and depend on many individual factors. Providers and parents should be aware of important considerations and best practices to promote the safe return to school for SOT recipients.¹³¹ Rates of ongoing SARS-CoV-2 transmission in both the community and school district will need to be taken into consideration. The age and developmental stage of the child will affect the capacity to follow safe distancing practices. Factors including comorbidities and the child's net level of immunosuppression, which varies with the time from SOT or any treatment for rejection, should be considered when deciding whether to return to school. Many medically stable children receiving low baseline immunosuppression could go back to school, as long as the school has adopted practical measures to prevent spread of SARS-CoV-2 based on guidelines detailed by the CDC and WHO.¹²⁸⁻¹³⁰ Most experts agree that while in school, it is important that children, particularly the SOT recipient, wear masks at all times, practice physical distancing, and have ready access to perform frequent hand hygiene.¹³¹ In some countries, a mask is recommended only when physical distancing in school is not possible. Siblings of SOT recipients should also be allowed to attend school but with similar attention to ensuring that the school is using appropriate precautions and continue to maintain the precautions while at home. Communicating with school nurses or directors to inform parents if another student or teacher becomes infected is also important. After discussion with transplant providers, at home virtual learning may be a better option in some higher risk SOT recipients.¹³¹

Consideration for younger children to go back to daycare even in small groups is challenging. Keeping preschool children at home may be preferred but is not always logistically possible. In addition to the positive contribution to the emotional and social development, this may be particularly important for parents who will have to go back to work and need childcare. This decision therefore depends on the family's circumstances. Caregivers should talk to the daycare center director ensuring they are working with the local health officials, taking all precautions recommended by the CDC or other national health authorities.

Ensuring that SOT recipients, their siblings, and all household contacts are up-to-date with age-appropriate vaccines will be important. The COVID-19 pandemic has led to a significant drop in routine vaccination rates in children, and continued provision of health care for all children is important.¹³² This is particularly true for receipt of the annual inactivated influenza vaccination for the SOT recipient and their family members. Parents should ensure that entry vaccination requirements with the school or daycare have not been disregarded during the pandemic.

Exposure to crowds or crowded environments is discouraged. Large family gatherings with groups of people from disparate geographic areas are not recommended because of the difficulty maintaining physical distancing. However, small family gatherings, when all members have been self-isolating, can be considered if the SOT recipient is receiving low level of immunosuppression. In such situations, it is important to ensure that no one has any symptoms, nor

had contact with a person with COVID-19 in the previous 14 days, and that there is low community SARS-CoV-2 prevalence. Sleep over parties are discouraged for pediatric SOT recipients as more intimate sharing of secretions and close contact are unavoidable. In general, smaller in-person gatherings are safer than large gatherings and outdoor gatherings are safer than indoor gatherings, but risk is optimally mitigated by keeping physical distancing, wearing masks, and performing hand hygiene.

When outside, it is still important to maintain six feet/two meters distance from others, frequently wash or sanitize hands, and avoid touching the face or eyes. The CDC recommends wearing a mask at all times in public places except for children under 2 years of age or those who cannot remove the mask themselves¹³³; the European CDC (ECDC) and WHO recommend to consider wearing a mask, especially in crowded areas.^{134,135} It is important to perform hand hygiene before and after placing the mask and to avoid touching the outside of the mask. Single-use masks should be thrown away after each use and cloth masks should be washed between each use. N95 masks are not required and should be preserved for healthcare professionals. Available evidence suggests that face shields are not as efficient in preventing SARS-CoV-2 transmission when used on their own, without concurrent mask use.^{133,135} Gloves are recommended only to clean surfaces but otherwise are not necessary; instead, performing hand hygiene, either by washing with soap and water or using sanitizer with >60% alcohol, should be enforced. These measures are also particularly important within the same household.

An often-difficult scenario for families of a child with a SOT is where a household contact is an essential worker and has SARS-CoV-2 exposure risk. For more heavily immunosuppressed SOT recipients due to rejection or recent transplant, availability of reassignment or family leave options for the family member who is an essential worker should be explored. Ideally, the worker should have access to and use appropriate personal protective equipment at all times. In addition, it is best to try to avoid contact with the family member until they have had the chance to change out of their work clothes and perform hand hygiene.

Scenario 5 summary statement: The obvious benefits of school attendance need to be weighed against the potential increased risk of exposure to SARS-CoV-2 for each child in the context of local virus transmission and family circumstances. Preventive measures such as careful hand hygiene, physical distancing, and wearing a mask can significantly reduce the potential of SARS-CoV-2 exposure among children after SOT and should be practiced in schools and daycare settings.

3.6 | Case scenario 6: Peri-transplant considerations when there is community transmission of SARS-CoV-2

A 14-year-old girl receiving dialysis is awaiting kidney transplantation when the COVID-19 pandemic hits her country. She and her parents ask if she should proceed with the transplant when an organ becomes available and her risk of possible SARS-CoV-2 infection through organ donation.

TABLE 3 Recommendations for SARS-CoV-2 testing in organ transplantation donors by transplantation societies

Donor type	SARS-CoV-2 scenario	The Transplantation Society [138]	AST [49]	European Centre for Disease Prevention and Control [137]
Deceased	No known SARS-CoV-2 infection	Negative RT-PCR/NAT before organ procurement (timing not specified)	<ul style="list-style-type: none"> At least one negative respiratory tract specimen RT-PCR/NAT performed ≤ 72 hours of procurement Some experts recommend a second test to be performed 12–24 hrs after the initial test, and ≤ 24–48 hours prior to procurement, when feasible. A second test could be considered when clinical suspicion is high and the first test is negative Thoracic organs: one of the two screening tests should be performed on a LRT sample (eg, tracheal aspirate or BAL sample), when feasible 	<ul style="list-style-type: none"> One negative RT-PCR/NAT, from upper or LRT, performed ≤ 72 hours of procurement In an area with sustained virus transmission, deceased donors without symptoms or diagnosis of COVID-19 should have a SARS-CoV-2 RT-PCR/NAT performed on BAL specimens collected ≤ 72 hours before organ procurement
Deceased	Confirmed SARS-CoV-2 infection	May consider if negative RT-PCR/NAT before procurement (timing not specified) and clinically recovered from COVID-19 prior to expiring	<ul style="list-style-type: none"> Consider only if ≥ 28 days from symptom resolution and negative RT-PCR/NAT Consider further evaluations for kidney and lung grafts 	Consider only if death ≥ 28 days from symptom resolution or ≥ 14 days from upper respiratory negative RT-PCR/NAT
Living	No known SARS-CoV-2 infection	Negative RT-PCR/NAT before procurement (timing not specified)	At least one negative respiratory RT-PCR/NAT performed ≤ 72 h of procurement	If SOT cannot be delayed, the donor's NP swab specimens should be tested for SARS-CoV-2 by RT-PCR/NAT ≤ 7 days before procurement
Living	Confirmed SARS-CoV-2 infection	May consider if ≥ 14 days since symptom onset AND ideally have two negative RT-PCR/NAT	<ul style="list-style-type: none"> Consider only if ≥ 28 days from symptom resolution and RT-PCR/NAT negative Consider further evaluations for kidney and lung grafts 	Consider only if ≥ 28 days from symptom resolution or ≥ 14 days from negative upper respiratory RT-PCR/NAT

In centers with ongoing SARS-CoV-2 community transmission, the decision of whether to proceed with transplantation ultimately will depend on the urgency of the need for the new graft. Clearly, it can be challenging to determine if it is safe to undergo an "elective" KTx during the COVID-19 pandemic. Receiving dialysis provides some freedom to optimize circumstances compared with children waiting for other organs where there are no other sustainable options for their progressive organ failure. However, organ transplantations have been safely and successfully performed in the US, Europe, and elsewhere during the COVID-19 pandemic. Accordingly, while decisions must be individualized with full discussion of risk/benefit, in the correct setting, undergoing a KTx for a child waiting while receiving dialysis may be the correct thing to do even during the pandemic.

Both SOT candidates and LD should follow prevention strategies to reduce exposure to SARS-CoV-2 in the immediate pre-SOT period. This includes complying with self-quarantine in the 14 days prior to living donation and avoiding exposure to potentially infected individuals. LD organ transplants offer the opportunity to plan for the transplant in a way that can maximize the ability to mitigate risks for both the recipient and for the donor, as such additional preventive efforts should be considered. The AST has published comprehensive recommendations for LD's testing and screening.¹³⁶ If feasible, the donor is encouraged to respect self-quarantine during 14 days prior to donation.¹³⁶ Ideally, others in their household or perhaps friends could complete certain tasks (eg, shopping) for the 2 weeks prior to planned donation. If anyone in their household develops any symptoms of illness, they should either minimize their contact with the potential donor within the house, or if possible find an alternative place for either the donor or the symptomatic household member to reside.

The risk-benefit of SOT during the pandemic should be discussed with the recipient, including the potential indirect effects of the COVID-19 pandemic such as decrease in total SOTs performed and potential for waitlist mortality.^{19,20} If it is decided to proceed with the SOT, screening and testing of both the candidate and the donor prior to surgery is warranted. In low prevalence settings, the risk of transmission through donation is very low when the donor has not had a COVID-19 exposure, is asymptomatic, and has a negative respiratory (most frequently NPS) RT-PCR performed within 3 days of organ donation. Most transplant societies strongly recommend universal screening of potential deceased donors before organ procurement. Guidance recommendations for donor SARS-CoV-2 testing are summarized in Table 3.^{49,137,138} Additional recommendations by region and society are available at <https://cdtrp.ca/en/covid-19-international-recommendations-for-odt/>. Timing of testing should also take into account the turn-around-time of PCR results, so that they are readily available before organ procurement. Performance of antibody testing would not be recommended at this time as the results would not provide any information about whether the donor is potentially infectious to the recipient.

The optimal time for donation after a potential donor had COVID-19 infection or exposure is unknown. In general, societies strongly recommend against the use of donors with active COVID-19^{49,137,138} and have different acceptance criteria for donors

who have recovered from COVID-19 (Table 3). Some societies recommend deferring donation in a previously SARS-CoV-2-infected donor until at least 28 days after symptom resolution and negative testing. One can argue that 28 days is a very long time and could be shortened in cases where an urgent transplantation is required, if certain criteria are met. Despite that the RT-PCR can remain positive for several weeks after resolution of infection,⁶⁴ it has been reported that the virus is not cultivatable if the RT-PCR cycle threshold is >24 and the patient developed symptoms >8–10 days prior.^{54,64} Severity of COVID-19 in the donor may also need to be considered, as cultivatable virus has been reported to be viable up to 32 days after the onset of symptoms in patients with severe COVID-19.¹³⁹ In addition, given pulmonary and renal dysfunction associated with COVID-19, but still uncertain long-term implications, additional considerations may be needed when accepting lungs or kidneys from COVID-19-positive donors. In cases where donors may not have been infected, but were exposed to a suspected or confirmed case of COVID-19 or are returning from a region with sustained COVID-19 transmission, some societies recommend avoiding donation for 14 days after the last exposure.^{137,138}

The possibility of donor-derived SARS-CoV-2 infection, including risk of blood transmission or graft involvement, should be discussed with the SOT candidate. During the COVID-19 pandemic in China, screening for SARS-CoV-2 RNA was performed on blood donors, with virus rarely detected among asymptomatic donors.¹⁴⁰ SARS-CoV-2 has been detected in cardiac, liver, brain, and kidney tissues.¹⁴¹ Also, a 6-month-old developed transaminitis early after living-donor liver transplantation where both donor (recipient's mother) and recipient subsequently tested positive for SARS-CoV-2, raising questions about possible donor-derived versus community-acquired transmission, given the relationship between the donor and the recipient.^{40,42} Despite the biologic plausibility, thus far, there are no confirmed instances of proven SARS-CoV-2 transmission through blood or organ donation.

In situations where the SOT candidate develops COVID-19, it is unknown what the optimal time period should be after acute infection where transplantation can safely proceed. Individuals should be deferred from proceeding with SOT until they are asymptomatic and ideally, until they have cleared the virus. The AST and TTS recommend to defer non-urgent SOT in candidates with COVID-19 until clinical improvement and documentation of two negative RT-PCR performed at least 24 h apart.^{49,138} Until additional data inform practice or definitive treatments are available, the risk of transplantation must always be weighed against the risk of deferring transplantation in an individual with acute or recent COVID-19.

Scenario 6 summary statement: The decision to perform a SOT during the COVID-19 pandemic must be individualized with full discussion of risk/benefit and take into account the urgency of transplantation, local virus transmission, and center resources. Guidance for both SOT candidates and donors are available to minimize the potential risk of donor-derived and peri-transplant SARS-CoV-2 infections, as data emerge, SOT deferment and screening recommendations may evolve.

3.7 | Case scenario 7: Approach to clinical appointments

The family of a 3-year-old child is being referred for a post-SOT routine appointment and are coming from a region with high COVID-19 prevalence. Should this medical visit be delayed or is it possible to institute preventive measures?

If the child is coming from a region with sustained SARS-CoV-2 transmission, they may not be allowed to travel depending on local and international travel regulations.¹⁴² In this case and if the child is otherwise medically stable, then the in-person consultation should be delayed and a telemedicine visit considered and encouraged, if possible.¹³⁶ Teleconsultation has emerged as a useful modality in allowing for continuity of care during the pandemic.^{143,144} If travel is authorized, then the child should ideally travel accompanied by a single, asymptomatic family member and both should quarantine for 14 days prior to the planned appointment. A SARS-CoV-2 RT-PCR could be considered on arrival and 48 h prior to the appointment in both the child and accompanying adult.

If the child is coming from a region with low or absent SARS-CoV-2 transmission or the appointment is deemed essential, then the child should travel accompanied by a single family member. Optimally, neither the child nor the accompanying adult should have had a recent exposure to COVID-19 and should not have symptoms compatible with COVID-19 in the 14 days preceding the planned appointment. SARS-CoV-2 RT-PCR testing prior to routine clinic appointments could be considered, though comparative data evaluating this strategy are n/a. Ultimately, whether the child and accompanying adult undergo SARS-CoV-2 RT-PCR testing will likely vary by transplant center and local epidemiology.

Scenario 7 summary statement: Each pediatric transplant center will need to develop their own policies around transplant appointments, taking into account national and international travel regulations, the potential for RT-PCR testing and recommendations for quarantining before the planned appointment in both the child and the accompanying adult. The importance and effectiveness of infection control strategies in preventing viral transmission highlight the need for strict enforcement of precautions, including masking and hand hygiene, in the clinic setting. Teleconsultations should be considered for elective appointments in medically stable SOT recipients whenever possible, particularly in areas with high SARS-CoV-2 community transmission.

3.8 | Case scenario 8: Additional prevention measures utilizing COVID-19 vaccine

A 16-year-old girl, recipient of a kidney transplant comes to her transplant clinic appointment. She wants to know if she will be eligible to receive the COVID-19 vaccine when it becomes available.

Currently, there is no approved vaccine against SARS-CoV-2 that is approved for use in SOT recipients. Unprecedented rapid developments are being observed internationally to produce a vaccine.¹⁴⁵ A vaccine tracker is available at <https://www.raps.org/news-and-artic>

les/news-articles/2020/3/COVID-19-vaccine-tracker. Various vaccines using different technologies (inactivated, live attenuated, DNA, viral vector, mRNA, RNA, recombinant protein) are currently in Phase 1–3 trials. Some major candidates are undergoing clinical evaluation.¹⁴⁵ At the time of this writing, inactivated, RNA, and viral vector vaccines have emerged as promising candidates and are being evaluated in phase III studies.¹⁴⁵ In phase 1/2 studies, mRNA-1273 and BNT162b1 RNA vaccines have been shown to be immunogenic without reported trial-limiting safety events.^{146,147} Adenovirus-based vaccines have also been shown to be safe and immunogenic in phase II studies.^{148,149} In phase 3 studies, mRNA and adenovirus-based vaccines have demonstrated promising results regarding vaccine safety and immunogenicity. However, it is currently unknown if these different vaccines will be safe and immunogenic in immunosuppressed patients. Pediatric data are also lacking and vaccine trials that include children down to 12 years of age are only just starting.¹⁵⁰ It will be critical to evaluate the immunogenicity and efficacy of a SARS-CoV-2 vaccine in SOT recipients as immunity to other vaccines may be diminished and wane in immunosuppressed patients, requiring booster doses.¹⁵¹ If indeed safe and immunogenic, additional studies will be needed to estimate duration of protection after vaccination in SOT recipients. As with other vaccines, a cocoon strategy is recommended so that close contacts and household members be appropriately vaccinated against SARS-CoV-2 as soon as possible in an effort to increase the potential protection of pediatric SOT candidates and recipients.

Scenario 8 summary statement: Preliminary data on SARS-CoV-2 vaccine safety and immunogenicity from early clinical trials in the general adult population are encouraging. It is yet unknown if these vaccines will be equally immunogenic, safe, and efficacious in SOT recipients and children. Ensuring inclusion of children in vaccine trials is a critical, yet unmet need.

4 | CONCLUSIONS

Now 11 months into the COVID-19 pandemic and until additional data emerge, it seems that pediatric SOT recipients are not at increased risk of acquiring SARS-CoV-2 infection nor developing more severe disease when compared with other immunocompetent children. In general, children may be less prone to severe COVID-19 infection than adults, possibly because of cross-reactive immunity with other human coronaviruses or because of a different distribution of ACE-2 receptors when compared with adults. Second, the iatrogenic immunosuppression provided after transplantation might contribute to reduce COVID-19 severity in SOT patients^{39,112} by dampening the innate immune response, the main driver of lung tissue damage during SARS-CoV-2 infection,³⁹ and by reducing T cells over-activation seen in lung tissues of patients with COVID-19 acute respiratory distress syndrome.¹⁵² The fact that pediatric SOT recipients may be more protected than their adult SOT counterparts against severe COVID-19 could also be related to the increased likelihood of

known risk factors for severe COVID-19 in the adult SOT setting, such as diabetes, hypertension, cardiovascular, and chronic respiratory disease comorbidities.¹⁵³ Additional SOT-specific data, that include children, are needed to better understand the pathophysiology of infection in the immunocompromised host, the optimal management of SARS-CoV-2 infection in pediatric SOT recipients, and the impact of the current pandemic on transplant outcomes. The emergence of multiple SARS-CoV-2 variants have raised concern for possible enhanced viral transmission and susceptibility to infection; at this time however, it remains unclear how that may change the paradigm of the current COVID-19 pandemic.^{154,155}

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTION

AGL and MIA reviewed and grouped the questions under distinct content categories that were then used to create the clinical scenarios. Each author performed at least one non-systematic review of the available literature and drafted the scenario(s) accordingly. Each author then critically reviewed at least another scenario. All authors critically reviewed the final version of the manuscript.

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