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ORIGINAL ARTICLE

C4 article: Implications of COVID-19 in transplantation

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A novel coronavirus has had global impact on individual health and health care delivery. In this C4 article, contributors discuss various aspects of transplantation including donor and recipient screening, management of infected patients, and prevention of coronavirus disease (COVID). Donor screening with SARS-CoV-2 nucleic acid testing (NAT) close to the time of procurement is recommended. Many programs are also screening all potential recipients at the time of admission. The management of COVID has evolved with remdesivir emerging as a new potential option for transplant recipients. Dexamethasone has also shown promise and convalescent plasma is under study. Prevention strategies for transplant candidates and recipients are paramount. Pediatric-specific issues are also discussed. Strategies for the psychological well-being of patients and providers are also imperative, in addition to future research priorities for transplantation.

KEYWORDS
clinical research/practice, infection and infectious agents, infection and infectious agents – viral, infectious disease, organ transplantation in general

1 | INTRODUCTION

SARS-CoV-2, a novel coronavirus, originated in China in late 2019 and has since caused an unprecedented pandemic with COVID-19 impacting almost all regions globally. Mortality is estimated to be 1%–3% and the predominant risk factor for mortality is age >60 years along with comorbid illnesses such as hypertension. Interestingly, children are less impacted although there are recent reports of a Kawasaki-like inflammatory syndrome that may be linked to COVID-19. Although the majority of severe disease involves the respiratory tract, other complications such as neurologic disease (confusion, cognitive difficulties, early strokes) as well as a hypercoagulable state can occur. Organ donation and transplantation have been greatly impacted by the pandemic. Donation rates significantly fell during the pandemic peaks although there was some geographic variability in this. Living donor transplantation was halted in many areas due to anticipated lack of hospital capacity and the concern for nosocomial transmission of virus. Significant concern was generated that high rates of severe COVID-19 disease would be seen in immunosuppressed transplant recipients. Indeed, transplant recipients appear to have a greater risk of mortality than the general population, although the exact increase in risk is difficult to ascertain as this has varied among studies and with time. Several case reports and case series of transplant recipients with COVID-19 have now been published and mortality ranges 18%–30%, although these studies are primarily reflective of a hospitalized population.[1–3] The potential bias in a more severely affected population needs to be taken into account during the interpretation of morbidity and mortality data. Serosurveys may shed more light in terms of how many transplant patients may have had milder disease courses. Notably, this is a rapidly changing situation, thus we are focusing on the current state of the disease.

This is the third in a series of C4 (defined as current, controversial, collaborative, and crowdsourced) articles that was first published by the *American Journal of Transplantation* in 2018. Given the uncertainties of the COVID-19 pandemic with regards to management of transplant patients and programs, we initiated a C4

See Appendix 1 for the full list of editors and contributors.

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article in order to better outline the issues. Editors chose seven topics that were relevant to COVID-19 in transplantation including the management of the infected transplant patient, donor screening, preventative measures in transplantation, transplant program management as well as how to protect the transplant team. We also specifically highlight pediatric issues as well as psychological and ethical considerations. The general epidemiology, virology, or immune responses of COVID-19 are discussed only as they are relevant to transplantation.

2 | METHODS

The editorial team (denoted by * in Appendix A) organized the article into relevant sections, highlighted some points to start the discussion, and invited several experts and members of the transplant community to contribute to the article via a public link to the Dropbox article (San Francisco, CA). Contributors were verified through Google docs and no contributor was excluded. The link was posted on the *American Journal of Transplantation* website and promoted by word of mouth. The article was open for 4 weeks from April 15, 2020 to May 15, 2020 for contributions. Similar to previous C4s, this article has 61 unique contributors or editors with 103 views by week 2 and an additional 73 views by week 4. After the second and fourth week, the versions were archived. Following this, the editors revised their sections and previous versions were available to view as Dropbox files (Week 2 archive: https://paper.dropbox.com/doc/COVID-19-IN-TRANSPLANTATION--A7vt0KqLGeSUwueIOyxINXIwAg-OT71bBK2J6GXhwSZxh6KJ and Week 4 archive: https://paper.dropbox.com/doc/COVID-19-IN-TRANSPLANTATION--A7suzteBq3PhrMLqxejKJnaRAg-r4nOoA7TYIU0iRiIDAZnf). The editors were responsible for summarizing their sections and ensured that similar contributions were combined and the appropriate references were added. Editors ensured that contributor thoughts were placed in the appropriate section to minimize duplication. This C4 differs from previous C4 articles since it tackles a topic where data continues to rapidly emerge. Therefore, some salient transplant and non-transplant studies published after the closure of contributions as well as those based on peer-reviewer comments were highlighted by the C4 editors. However, the message provided by the contributors was retained.

3 | DISCUSSION

3.1 | Diagnostics for COVID

While some clinical symptoms are more strongly associated with COVID-19, such as loss of smell or taste, most are not pathognomonic of the infection. As such, diagnostics are needed to confirm infection with SARS-CoV-2. Currently diagnostics are focused on clinical assessment, detection of virus by nucleic acid testing (NAT), and detection of antibodies to SARS-CoV-2. Limitations of reagents, testing capacity, test components, especially swabs, and testing locations still exist.

3.1.1 | Molecular diagnostics

Real-time polymerase chain reaction (RT-PCR), using a laboratory developed test (LDT) or a commercial assay, is the main diagnostic approach at most centers. Assays utilize different viral targets (RdRp, E gene, spike, Open Reading Frame [ORF] 1a, and nucleocapsid [N]).[4]

The underlying kinetics of viral infections are key to understanding PCR test performance. Viral replication begins 24–48 hours prior to symptom onset and peaks at days 3–5 after symptom onset.[5,6] Patients with more severe infections typically have higher viral loads in all locations and shed virus longer (21 vs. 14 days).[7,8] Higher viral loads are noted with increasing age. While viral shedding is prolonged for many patients, for those with mild disease, culturable virus is generally no longer detected when the viral load drops below 10^6 copies or Ct (cycle threshold) value >34 which generally occurs around day 8 after symptom onset.[9,10] Virus has been detected outside the respiratory tract, including the blood and stool, but these sites are not typically sampled for diagnostic purposes.[11]

False-negative PCR testing from upper airway samples is more common very early and late after infection. Likewise, patients with pneumonia who may have detection of virus from lower but not upper respiratory tract samples have been described. False-negative PCR testing may occur with worsening clinical status later in the disease course.[12] As discussed below, serologic testing for SARS-CoV-2, may be useful in this setting. Across studies, samples from the lower respiratory tract have consistently had both higher viral loads and a higher percent positivity rate versus nasal samples (93% vs. 63%).[13,14] Several studies have demonstrated saliva to yield excellent sensitivity and slightly higher viral loads than nasal swab with significant ease in collection.[7,15]

Several studies have demonstrated the ability to detect virus from asymptomatic and presymptomatic patients. Virus in these patients can frequently be cultured suggesting presence of transmissible virus.[16,17]

In the United States, all current SARS-CoV-2 assays are being used under Emergency Use Authorization (EUA, https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations). Without a gold standard of diagnosis, it is difficult to define these test characteristics and the performance of the assays approved under the EUA has not been widely studied. The few studies that have been completed suggested excellent sensitivity and specificity with agreement across most assays; most have noted slightly lower sensitivity with the Abbott ID Now system.[18-21]

3.1.2 | Radiological assessment

Several studies have suggested that CT scans of chest are more sensitive than upper respiratory PCR testing early in the disease course.[22,23] Findings are typically nonspecific and testing poses risk of exposure to radiology staff, so current guidelines generally do not recommend imaging for the diagnosis of COVID-19 (https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection). However, in cases of high suspicion for COVID-19 lower respiratory tract disease and repeated PCR negativity, a CT chest can be done although radiologic findings of COVID-19 are not specific.

3.1.3 | Serologic testing

Measuring antibody responses to SARS-CoV-2 may be useful for clinical, epidemiologic, therapeutic, and prevention efforts. In particular, serologic testing may have a role in (1) detection of PCR-negative cases, especially for patients who present late with viral loads below the detection limit of RT-PCR assays; (2) identification of convalescent plasma donors if quantitative assays are used; (3) contact tracing after a suspected exposure; (4) epidemiologic studies of disease prevalence in the community; and (5) verification of vaccine efficacy. However, serologic testing is also fraught with pitfalls due to technical and analytical heterogeneity, especially when tests are not rigorously validated (leading to false positives and false negatives) and when testing is applied to a mass scale in low prevalence settings (leading to false positives). The benefits and approaches of serology have been reviewed extensively elsewhere.[4]

IgM antibodies begin to develop 3–7 days after symptom onset with IgG developing on symptom days 11–14; most are positive by 3 weeks after symptom onset.[24] Titers typically decline after 2 months, as they do with many infections, but the duration of protection is not well studied to date. Furthermore, assays are just beginning to be validated and current tests have a wide range of sensitivity and specificity. Few of the available tests confirm the detection of neutralizing antibodies.

3.2 | Management of the COVID+ transplant recipient

Patients infected with SARS-CoV-2 can have dramatically different courses of illness. Risk factors for severe disease include comorbidities such as obesity, diabetes, hypertension, renal disease, cardiovascular disease, chronic respiratory disease, and cancer. Risk factors for mortality include older age, higher Sequential Organ Failure Assessment score, and d-dimer >1 mcg/ml on admission.[25] Some reports suggest that transplant recipients are at greater risk of complications of COVID-19 owing to immunosuppression whereas others infer that the immunosuppression has a limited impact and it is the comorbidities that drive the risk.[26,27]

Optimal strategies for antiviral and immune-based therapies have not been established; all drug therapies remain investigational. Over 1200 clinical trials worldwide and over 250 in the United States are recruiting or have been completed (covid-trials.org), evaluating over 30 agents that may have efficacy against SARS-CoV-2.[28] Treatment guidelines for COVID-19 are published by the National Institutes of Health,[29] and management varies by severity of illness (Table 1).

Asymptomatic and mild infections can be managed at home. Priorities include close monitoring for clinical deterioration as well as isolation in order to prevent transmission to others. Acetaminophen can help manage fever and myalgia. Nonsteroidal anti-inflammatory drugs are not known to be problematic in patients with COVID-19,[30] although they are often avoided to prevent nephrotoxicity in transplant recipients taking concomitant calcineurin inhibitors. Despite initial reports, renin-angiotensin-aldosterone system inhibitors should be continued in patients in stable condition.[31,32]

Moderate and severe disease requires hospital admission for supportive care. At a minimum, routine monitoring should assess for fever, myalgia, GI symptoms, respiratory status, renal dysfunction, myelosuppression, thrombosis, and psychiatric assessment. Hospitalized adults should receive venous thromboembolism prophylaxis. Empiric broad spectrum antibiotics should be given if bacterial pneumonia or sepsis is suspected, with daily reevaluation and de-escalation or discontinuation as soon as able. As per the RECOVERY trial, patients who require supplemental oxygen or mechanical ventilation may derive a mortality benefit from dexamethasone.[33,34] This benefit appears limited to patients who are more

TABLE 1 COVID-19 categories of illness (assumes SARS-CoV-2 PCR is positive)

Asymptomatic or presymptomatic infection	Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic or antigen test, but have no symptoms
Mild illness	Individuals who have any of various signs and symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) >94% on room air at sea level
Severe illness	Individuals who have respiratory frequency >30 breaths per minute, $SpO_2 \leq 94\%$ on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300, or lung infiltrates >50%
Critical illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

Note: National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8/02/2020.

than 7 days from symptom onset. In the setting of a dexamethasone drug shortage, equivalent doses of prednisone, methylprednisolone, or hydrocortisone should be considered.[29]

Therapies used in the treatment of COVID-19 are the same in transplant recipients as in non-transplant patients (Table 2). Several potential antiviral therapies used early in the pandemic including hydroxychloroquine[35–37] and lopinavir/ritonavir have been found ineffective and should not be used to prevent or treat infection in transplant patients.[38] The most promising antiviral at this time is remdesivir, which has been fully or conditionally approved by health authorities around the world based on clinical trials.[39–41] It is currently available in the United States through an FDA Emergency Use Authorization for select patients with severe COVID-19.[42] Note that the data on anti-viral therapies are primarily derived from a non-transplant population. The FDA has also issued guidance on the use of convalescent plasma,[43] rendering it classified and regulated as an investigational product. For adults, COVID-19 convalescent plasma is available as a treatment option in the United States through an expanded access program (uscovidplasma.org). Detailed information for health care providers, patients who have recovered from COVID-19 infection and are willing to donate plasma, and for patients who are considering this treatment is available at https://ccpp19.org/. It is unknown if convalescent plasma will be associated with an increased risk of rejection due to off-target effects.

Accumulating evidence suggests that the cytokine storm triggered by SARS-CoV-2 may be responsible for severe lung injury.[44] Several case series have shown a benefit for IL-6 inhibition with tocilizumab in reducing mortality in ventilated patients or reducing progression to mechanical ventilation in severe disease.[45–47] In a cohort of 80 kidney transplant patients treated with tocilizumab, there was a decline in inflammatory markers.[48] However, phase III studies for IL-6 inhibition have not demonstrated clinical efficacy[49,50]; studies of other agents are under way and the tocilizumab arm of the RECOVERY trial is yet to be analyzed.[51] Nevertheless, the optimal use of these agents may depend on the correct timing of administration in the inflammatory cascade. It is currently unknown whether or not interruption of transplant immunosuppression may exacerbate the inflammatory response to SARS-CoV-2 and have a detrimental effect. There is general agreement that there is no chemoprophylaxis, and no need to modify or stop immunosuppression in asymptomatic or mild disease. Decreasing immunosuppressant medications may be considered according to the severity of illness, but complete withdrawal of immunosuppression has not been recommended.[52] The optimal way to manage immunosuppression remains unknown. Many experts reduce the antimetabolite first followed by the calcineurin inhibitor. There are no clear target trough levels although these may depend on the organ transplanted as well as time from transplant. More recently, dexamethasone is shown to reduce mortality in hospitalized COVID patients although it is unclear how beneficial this strategy would be in transplant recipients given the ongoing immunosuppression and potential for secondary infections.[33]

3.3 | Prevention strategies for the transplant recipient

Prevention methods for COVID-19 are likely familiar to transplant patients, who were already encouraged to avoid unnecessary community and health care exposures through social distancing and infection control, practice enhanced hygiene, and optimize immunosuppression and comorbidities. It is not yet known whether alterations in social distancing measures (eg, ongoing distancing even if restrictions lifted for general population) would be more effective for this population. Universal face masks are now standard in guidelines for infection prevention. This strategy was studied in the hematopoietic stem cell transplant population, where a universal surgical mask policy was implemented for all individuals with direct patient contact; respiratory viral infections decreased from 10.3% in the premask period to 4.4% in the mask period ($P < .001$).[53] Extrapolating this concept to SOT recipients, their caregivers, and contacts is a recommended strategy during the COVID-19 pandemic.

Whether to screen asymptomatic transplant patients remains an area of debate; some programs screen all patients admitted to a transplant ward regardless of symptoms, while others perform targeted screen only for those undergoing transplant or treatment of rejection. Pre-admission telephone screening by symptom checklist can help with triage; persons under investigation for COVID-19 should be cohorted away from the transplant floors, when possible. Ideally, testing of asymptomatic patients and donors should be performed to avoid transmission to transplant recipients and health care workers. Recommendations for universal screening should be based on the local epidemiology, testing capacity of the laboratory, and access to reliable performing platforms.

Other preventative measures include optimizing comorbidities such as hypertension and diabetes. Patients can be encouraged to monitor blood pressure at home, which has been shown to better correlate with 24-hour ambulatory blood pressure monitoring than office blood pressure in kidney transplant recipients[54] and overall better blood pressure control.[55,56] Similarly, optimizing diabetes control through more intensive home monitoring, data collection, and telemedicine is encouraged. Social distancing has resulted in less exercise for many, augmenting these comorbidities; safe methods to exercise and walking should be encouraged. Optimizing patients' self-care at home for common medical comorbidities may enhance both current and future effective medical care. The role of pre-emptive changes in immunosuppression, such as avoiding induction immunosuppression to prevent severe COVID-19 is unknown. For example, in kidney transplantation, literature suggests basiliximab is similar to anti-thymocyte globulin for induction therapy in non-sensitized patients or sensitized patients without donor-specific antibodies.[57,58] Some programs have enhanced infection control in their belatacept infusion centers[59] or increased use of home infusions, while others have switched belatacept to non-infusion immunosuppression. There may be risk of transmission of virus associated with blood product transfusions,[60] suggesting we should avoid unnecessary transfusions until we have more testing of blood products and safety data.

TABLE 2 Current therapies for severely and critically ill patients with COVID-19

Drug	Mechanism of activity	Dosing	Risks and precautions	Clinical trial highlights	NIH Guideline Recommendation
Remdesivir	Binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription	Obtain drug through FDA Emergency pathway 200 mg IV on day 1, then 100 mg IV daily for 5–10 days Dose adjustments: • Renal impairment: avoid use if eGFR <30 ml/min or dialysis • Hepatic impairment: avoid use if ALT or AST are >5 times ULN	• Nausea, vomiting • Transient elevations in AST or ALT • Mild, reversible PT prolongationThe IV formulation is made with cyclodextrin, which is renally eliminated and accumulation may cause nephrotoxicity	Beigel et al[39]: • Median recovery time was 11 days for remdesivir versus 15 days for placebo ($P < .001$) • Mortality at 14 days was 7% for remdesivir versus 12% for placebo (p = ns)	• Because supplies are limited, prioritize for use in hospitalized patients with COVID-19 who require supplemental oxygen but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO (B1) • Insufficient data to recommend either for or against use in patients with mild or moderate COVID-19
Dexamethasone	Anti-inflammatory effects of corticosteroids may prevent or mitigate the systemic inflammatory response in patients with severe COVID-19	6 mg IV/PO daily for up to 10 days	• Hyperglycemia, secondary infections, psychiatric effects, avascular necrosis	Recovery trial[33] • Mortality in mechanically ventilated patients was 29% on dex versus 41% with usual care alone • Mortality in patients requiring oxygen was 23% on dex versus 26% with usual care alone	• Recommended for the treatment of COVID-1list9 in hospitalized patients who are mechanically ventilated (A1) and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated (B1) • Recommends against use for the treatment of COVID−19 in patients who do not require supplemental oxygen (A1)
Convalescent plasma, and SARS-CoV-2 immune globulins	Plasma from donors who have recovered from COVID-19 includes antibodies to SARS-CoV-2; both products may help suppress the virus and modify the inflammatory response	Follow the FDA EIND guidance, or use the national expanded access program	• Risk for transfusion reactions (fever, anaphylaxis, lung injury, infectious transmission) • Theoretical risk of antibody-mediated enhancement of infection	Valk et al[95] • Very low-certainty evidence on effectiveness and safety	• Insufficient data to recommend either for or against use for the treatment of COVID-19
IL-1 inhibitors (eg, anakinra)	Endogenous IL-1 is elevated in COVID-19 and CAR-T mediated CRS	Varies; the IV formulation is not approved by the FDA	• No significant safety concerns in sepsis trials • Increased infection rates with prolonged use	Limited data	• Insufficient clinical data to recommend either for or against use of these agents for the treatment of COVID-19 (AIII)

(Continues)

TABLE 2 (Continued)

Drug	Mechanism of activity	Dosing	Risks and precautions	Clinical trial highlights	NIH Guideline Recommendation
IL-6 inhibitors (eg, tocilizumab, sarilumab)	Blocks inflammatory pathway via IL-6 receptor inhibition	Tocilizumab: 8 mg/kg (max 800 mg) IV ×1 or 324 mg SQ ×1; a second dose may be given within 24 h if no improvement Sarilumab: 400 mg IV ×1; the IV formulation is not approved by the FDA	• Infusion-related reactions • GI perforation • Changes in neutrophils, platelets, lipids, and liver enzymes • HBV reactivation	Limited data	• Recommends **against** use for the treatment of COVID-19, except in a clinical trial (B1)

Note: Rating of recommendations: A = strong; B = moderate; C = optional. Rating of evidence: I = one or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II =one or more well-designed, nonrandomized trials or observational cohort studies; III =expert opinion.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAR-T, chimeric antigen receptor T cell; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EIND, emergency investigational new drug; FDA, Food and Drug Administration; GI, gastrointestinal; HBV, hepatitis B virus; IV, intravenous; PO, oral; PT, prothrombin time; SARS, severe acute respiratory syndrome;SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SQ, subcutaneous; ULN, upper limit of normal.

Thus far, there is no known effective antiviral prophylaxis or vaccine. Data on the immunogenicity, effectiveness, and side effects of future vaccines will be needed in the transplant population. Based on prior vaccine experience, transplant recipients may need more or higher doses of vaccine.[61]

3.4 | Approaches to donor screening

The COVID-19 pandemic has caused substantial decreases in transplantation across the world, although the actual decrement has varied with time and geography. Fear of hospital acquired infection of living donors or newly transplanted recipients, unknown risk of donor-derived infection, lack of intensive care unit beds, shortage of dialysis supplies and medications, blood product scarcity, lack of adequate personal protective equipment, testing limitations and stressed or overwhelmed health care systems have all contributed to the decrease.[62,63] Evaluation of potential organ donors by organ procurement organizations (OPO) is also challenging given the requirement for ICU beds for donor management, need for rapid turnover and other issues as mentioned above. As the pandemic continues, transplant centers and OPOs have learned ways to adapt to the challenging environment.

Although there is a potential risk of donor-derived SARS-CoV-2 transmission through organ transplantation, no definitive cases have been reported to date. Lung transplant may be the most likely to transmit the virus, but SARS-CoV-2 has been detected by nucleic acid testing in blood, urine, and stool[9,11,60,64,65] as well as in non-lung tissue during autopsy, including heart and kidney tissues.[66-68] The transmissibility of virus from these tissues is unknown.

Most transplant societies world wide have recommended that all organ donors are screened for clinical symptoms and risk of COVID-19 exposure and tested for SARS-CoV-2 prior to organ procurement. This is to prevent the possible transmission of infection but also to protect the transplant team. The American Society of Transplantation recommends all organ donors are screened "epidemiologically and by clinical history for suspected COVID-19…[and recommend] … testing of at least one sample from the respiratory tract by NAT … within 3 days of procurement whenever feasible."[69]

Donor PCR tests should be sent from respiratory tract samples. For deceased donors, it is generally recommended to test samples from both the upper respiratory tract (nasopharyngeal and/or oropharyngeal swabs) and the lower respiratory tract (sputum, bronchoalveolar lavage, tracheal aspirate, pleural fluid, and/or lung biopsy) where possible, based on data suggesting an increased screening sensitivity using lower respiratory tract samples as compared with upper respiratory tract samples.[5,70,71] The potential of false-negative NAT results of samples with low viral loads needs to be carefully considered when collecting samples and deciding on organ procurement from a high-risk donor with negative NAT results.[72] At times, repeat testing may be helpful, especially if the donor has not been tested within 48 hours of planned procurement.

For living donors, screening for COVID-19 infection should also be performed, at a minimum with a clinical screen and with NAT/PCR on a single upper respiratory tract sample; the timing of this depends on the individual donor. If testing is negative, the living donor should be asked to socially distance as much as able and wear a mask when around others until the transplant occurs, especially within 14 days of the planned surgery. Ideally, a repeat clinical screening and PCR test should be performed within 48 hours of donation.[69]

The optimal deferral period is still not known for living donors who test positive for SARS-CoV-2 infection or for deceased donors who have recovered from COVID-19. Based on the average duration of PCR positivity (approximately 20 days),[25] the American Society of Transplantation (AST) suggests waiting at least 28 days from resolution of symptoms (for living donors) before organ donation can be considered safe. AST recommends declining organs from donors with active COVID-19 infection, SARS-CoV-2 detected on testing as part of the donor hospital or OPO evaluation or who are less than 28 days from resolution of clinical symptoms of a past COVID-19 infection.[69] This is always with the caveat of balancing the risk of deferring transplantation for a specific recipient.

The best use of serology assays, mainly used for the detection of past infection, has not been established for organ donor screening. It is unlikely that serology for SARS-CoV-2 will be useful to determine donor suitability since it is similar to other viruses that cause acute infections and do not establish latency. Nevertheless, once the performance characteristics of the serology assays are better established, the role of donor serology will become clear.

Given the evolving nature of the pandemic and a need for more data upon which to base permanent policy decisions, there is currently no OPTN policy requiring donor testing, but data are being collected (https://optn.transplant.hrsa.gov/covid-19/). The OPTN has put together an Emergency Policy Package to provide additional flexibility during the COVID-19 crisis ("COVID-19 Emergency Policy Package" [https://optn.transplant.hrsa.gov/media/3716/covid-19_emergency_policypackage_and_minibrief.pdf]). The issues addressed include modification of kidney waiting time, data submission requirements, timely collection of data, and reporting requirements after living donation of kidney or liver.

3.5 | Considerations of inpatient and outpatient transplant activity

3.5.1 | Reductions in new transplant activity

Transplant activity during the COVID-19 pandemic has been significantly curtailed.[73] For example, the majority of US transplant programs (71.8% on a national survey of transplant centers conducted March 24–31, 2020) completely suspended their living donor kidney transplant programs and most placed modifications and restrictions on deceased donor kidney transplantation (>80% of responding programs).[74] The reasons for this are multifactorial and include (1) issues related to hospital infrastructure and resources to allow treatment of COVID patients, (2) avoidance of iatrogenic immunosuppression during a time where community or hospital exposure in the transplant recipient is a possibility, (3) concerns regarding living donor safety, (4) concerns related to the potential for COVID transmission via the organ, and (5) an an overall decrease in deceased donation. However, in most situations, transplant activity should not be considered "elective" (https://www.cms.gov/ –March 18, 2020). A possible phased approach to transplant activity reduction was outlined in Kumar et al.[62]

3.5.2 | Reductions and changes to outpatient activity

Most programs modified outpatient transplant clinics early in the pandemic as hospitals prepared for increasing numbers of COVID patients. Deferral of routine long-term follow-up visits or a change to virtual platform (telehealth or telephone) is a relatively simple strategy to avoid in-person hospital ambulatory visits. During the COVID pandemic, many jurisdictions have facilitated virtual care platforms and specifically two-way video technology to improve the virtual experience. The expansion of reimbursement options for telehealth services is also of critical importance in ensuring the success and sustainability of virtual models of care. In addition, virtual platforms are useful for many aspects of transplant evaluation, waitlist candidate follow-up and early posttransplant follow-up care. However, as the pandemic subsides, transplant programs will face a back-log of clinic patients. Programs may need to create additional clinics and continue to leverage the potential of telemedicine to get caught up with the number of patients awaiting to be seen.

3.5.3 | Approach to phasing up transplant activity

The decision of when and how to transition from a state of low transplant activity toward a return to "normal" activity is challenging. Transplant programs will need to implement nuanced and individualized approaches based on local SARS-CoV-2 activity and health care system burden.

However, a relatively rapid phasing up of transplant activity is important in order to meet the needs of our patients with advanced organ disease, as well as honor the life-saving gifts of donors. Timing of such initiation is likely to look very different across the country and internationally based on the local level of COVID-19 impact. Scheduling living donor transplants that have been postponed or canceled may be more difficult if competing for OR time and resources with other surgical specialties such as cancer and cardiac surgery where many scheduled patients may have faced unacceptable delays.

Conditions that should be met as phase up is contemplated include (1) processes to ensure safety of recovery teams, (2) robust donor screening process, (3) adequate infrastructure and

resources in the transplant hospital (OR availability, ICU capacity, work-force, PPE), (4) capacity for outpatient posttransplant follow-up, and (5) appropriate recipient consent and communication processes. A possible phase up plan is shown in Table 3 along with conditions that could allow movement from one phase to another. A multi-disciplinary approach including physicians, staff, hospital leadership, public health and epidemiology etc. is necessary in order to individualize the approach that each center takes regarding the timing of resuming transplant activities. In addition, for transplant hospitals that continue to have a high COVID patient burden, "COVID-free" zones for transplant patients (and living donors) are desirable in order to minimize the risk of nosocomial acquisition.

3.6 | Protecting the transplant team

Health care personnel (HCP) represent 4%–19% of those infected with SARS-CoV-2.[75–77] HCP involved in transplantation is at risk of becoming infected with SARS-CoV-2 in the health care setting from other HCP, transplant candidates, recipients, and SOT donors.[78] Transplant centers must develop and implement effective strategies to mitigate the risk of HCP infection.

In the outpatient setting, non-urgent encounters and procedures could be deferred. Telehealth and telemedicine are now available and may be enhanced by home digital monitoring programs. They could also be used to provide medical care to stable SOT recipients and those with COVID-19 during the isolation period. All SOT candidates, recipients and living donors should wear a facemask during visits to the health care facility and be screened for symptoms compatible with COVID-19 prior to entry. This evaluation should ideally occur prior to the visit. Those screening positive will require evaluation and testing to rule out COVID-19 in a designated area with the appropriate precautions.[79] SOT recipients regularly undergo procedures. Aerosol generating procedures (AGP) (eg, intubation, bronchoscopy, gastrointestinal endoscopy, nasal and sinus endoscopy, swallowing evaluations, and administration of nebulized solutions) pose the greatest risk of SARS-CoV-2 transmission. In addition to symptom screening, many transplant hospitals have instituted routine testing prior to these procedures.

3.6.1 | Preventing transmission from patients with suspected or confirmed COVID-19

Patients with suspected or confirmed COVID-19 should be placed in a single-patient room with the door closed and a dedicated bathroom. Airborne infection isolation rooms (single-patient, negative-pressure room) should be reserved for patients who will undergo an AGP. To limit HCP exposure, facilities could designate a unit within their facility to care for patients with known or suspected COVID-19. With the same goal, HCP should be designated to work specifically in these units whenever possible.[79] HCP evaluating patients with suspected or confirmed COVID-19 should adhere to standard precautions and use a respirator (or a facemask if a respirator is not available), gown, gloves, and eye protection. If a patient with suspected or confirmed COVID-19 undergoes an AGP, the number of HCP in the room should be minimized and those present should wear a respirator.

3.6.2 | When to discontinue isolation for persons with COVID-19

In a study of 56 patients from Wuhan, China the median time between onset of symptoms to NP RT-PCR negative was 24 days.[80] SARS-CoV-2 has not been cultured more than 9 days after the onset of symptoms in patients with mild disease; albeit the sample size of these studies was small.[9,16] A larger study that included 129 patients, 89 (69%) requiring intensive care and 30 (23%) immunocompromised, described that infectious virus could be detected up to 20 days from upper respiratory specimens.[81] A large contact tracing study demonstrated that high-risk household and hospital contacts did not develop infection if their exposure to a case patient started 6 days or more after the case patient's illness onset.[82] The Korean CDC cultured 108 patients who retested positive at a median time of 44 days; all cultures were negative. The investigation also traced 790 contacts. Three new cases of COVID-19 were identified; all had other known exposures.[83] Collectively, these data prompted an update to the CDC guidelines regarding the duration of isolation and precautions for adults with COVID-19 (Table 4). The revision favors a symptom-based strategy although a test-based strategy could be considered in consultation with infectious diseases experts for severely immunocompromised patients.[84] Regardless of the strategy used retesting after discontinuation of isolation is discouraged.

There are little data to guide the decision to discontinue isolation in SOT recipients. There is concern, based on data with influenza, of prolonged infectivity with SARS-CoV-2 but this has not been confirmed.[85] The optimal strategy (time or test based) and timing of discontinuation of isolation for SOT recipients with COVID-19 is unknown. A time-based strategy could increase the risk of transmissions. This risk can be minimized in the health care setting by a universal mask policy. A test-based strategy, in SOT, is limited by the availability of testing and lack of correlation between positive RT-PCR and infectivity. The duration of isolation proposed by the CDC for non-immunocompromised patients may also increase the risk of transmission if a longer duration of infectivity is ultimately confirmed. A longer duration of isolation could potentially delay required medical care.

TABLE 3 A potential guidance to phasing up transplant activity during the pandemic

Transplant restart level	Description of conditions	Description of activity
Restart phase 1: limited increase in activity	A significant flattening of the pandemic curve is observed in the jurisdiction. This includes a stable number of new cases; and some stabilization in ward/ICU bed utilization	• Kidney TRANSPLANT ○ No living donor activity; ○ Allow NDD-SCD deceased donors to recipients based on waitlist priority ○ Medically urgent and HSP recipients (PRA >= 95%) eligible for all NDD-SCD, NDD-ECD and selected DCD donors • Liver transplant ○ Living donor activity for moderate to severe sick recipients only ○ Deceased donor activity; NDD; DCD < age 50 • Heart transplant ○ High status heart patients only; defer if stable on LVAD • Lung transplant ○ High status patients only; NDD donors • Pancreas and kidney-pancreas transplant ○ NDD- SCD and DCD < age 35 activity for SPK; no PAK or PTA activity • Small bowel transplant ○ No activity unless combined with liver
Restart phase 2: moderate increase in transplant activity	The number of new COVID cases is flat or decreasing for a period of time (eg, >2 weeks) and ICU and ward bed utilization has been at a stable level for >2 weeks at the transplant hospital	• Kidney transplant ○ Very selected living donor activity (imminent dialysis in a pre-emptive transplant); ○ Allow NDD-SCD, NDD-ECD, and selected DCD donors to recipients based on waitlist priority • Liver transplant ○ Living donor activity for moderate to severe sick recipients only ○ Deceased donor activity as normal for NDD and DCD • Heart transplant ○ High status; low status only if institution/ICU capacity allows • Lung transplant ○ Moderate to high status recipients, NDD, DCD donors • Pancreas and kidney-pancreas transplant ○ NDD-SCD; DCD < age 50 activity for all SPK and; PAK recipients; no PTA activity • Small bowel transplant ○ No activity unless combined with liver
Restart phase 3: near normal transplant activity	Prolonged stability and/or decreases in COVID activity is observed along with prolonged stability or decreases in hospital ICU/ward bed utilization. ICUs are running consistently below capacity at transplant hospital	• Kidney transplant ○ A slow phase up of living donor activity ○ Resume regular jurisdiction-based allocation algorithm for NDD and DCD deceased donor kidneys • Liver transplant ○ Living donor activity as normal with some priority to sicker recipients ○ Deceased donor activity as normal • Heart transplant ○ Normal activity • Lung transplant ○ All status patients, NDD, DCD donors as per normal criteria • Kidney-pancreas transplant ○ Normal activity • Small bowel transplant ○ Deceased donor activity as normal

Abbreviations: NDD, neurological determination of death; DCD, donation after cardiocirculatory death; ECD, exceptional criteria donor; SCD, standard criteria donor; PRA, panel reactive antibody; SPK, simultaneous pancreas-kidney; PAK, pancreas after kidney; PTA, pancreas transplant alone; LVAD, left ventricular assist device.

[a]Modified from Trillium Gift of Life Network (TGLN) Ontario criteria for phased restart of transplant activity. The Table is provided only as a rough guidance to programs and should take into account other jurisdictional issues.

3.6.3 | Measures to prevent transmission of SARS-CoV-2 from HCP

To minimize the spread of SARS-CoV-2 from one HCP to another, most centers have adopted the following measures.[79] HCP are asked to monitor themselves for symptoms compatible with COVID-19 and promptly contact infection control if symptomatic. All HCP are screened for COVID-19 compatible symptoms upon entering the health care facility. Despite these recommendations, a study from Washington, revealed that HCP worked for an average of 2 days

TABLE 4 CDC - duration of isolation and precautions for adults with COVID-19[a]

Recommendations
1. Duration of isolation and precautions • For most persons with COVID-19 illness, isolation and precautions can generally be discontinued 10 days *after symptom onset*[1] and resolution of fever for at least 24 h, without the use of fever-reducing medications, and with improvement of other symptoms. o. A limited number of persons with severe illness may produce replication-competent virus beyond 10 days that may warrant extending duration of isolation and precautions for up to 20 days after symptom onset; consider consultation with infection control experts. • For persons who never develop symptoms, isolation and other precautions can be discontinued 10 days *after the date of their first positive RT-PCR test for SARS-CoV-2 RNA*. 2. Role of PCR testing to discontinue isolation or precautions • For persons who are severely immunocompromised, a test-based strategy could be considered in consultation with infectious diseases experts. • For all others, a test-based strategy is no longer recommended except to discontinue isolation or precautions earlier than would occur under the strategy outlined in Part 1, above. 3. Role of PCR testing after discontinuation of isolation or precautions • For persons previously diagnosed with symptomatic COVID-19 who remain asymptomatic after recovery, retesting is not recommended within 3 months after the date of symptom onset for the initial COVID-19 infection. In addition, quarantine is not recommended in the event of close contact with an infected person. • For persons who develop new symptoms consistent with COVID-19 during the 3 months after the date of initial symptom onset, if an alternative etiology cannot be identified by a provider, then the person may warrant retesting; consultation with infectious disease or infection control experts is recommended. Isolation may be considered during this evaluation based on consultation with an infection control expert, especially in the event symptoms develop within 14 days after close contact with an infected person. • For persons who never developed symptoms, the date of first positive RT-PCR test for SARS-CoV-2 RNA should be used in place of the date of symptom onset. 4. Role of serologic testing • Serologic testing should not be used to establish the presence or absence of active SARS-CoV-2 infection or reinfection.

Note: Adapted from CDC Coronavirus Disease 2019 – Duration of Isolation and Precautions for Adults with COVID-19.

Abbreviations: COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; RNA, ribonucleic acid; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]These recommendations are not specific for immunosuppressed patients and it is unknown if it can be extrapolated to this population.

after the onset of symptoms.[86] Furthermore, it noted that even expanded symptom-based screening fails to identify all infected HCP. For this reason, universal masking of HCP within the health care facility is strongly recommended.

3.6.4 | Protecting the Organ Procurement Organization HCP

The HCP of organ procurement organizations (OPOs) are also at risk of acquiring SARS-CoV-2. The first line of protection is the screening that is recommended for all patients before entering a health care facility.[79] Regardless, the OPO team should review the donor electronic health record and independently perform clinical screening for epidemiological risk factors and symptoms compatible with COVID-19. In addition to SARS-CoV-2 donor testing, this information serves the dual purpose of protecting the OPO HCP and minimizing the risk of a SARS-CoV-2 donor-derived infection.

3.7 | Pediatric-specific issues

SARS-CoV-2 infection in the pediatric population has been associated with mild disease even in very young children.[87] However, reports of clusters of unusual and sometimes severe conditions in children that begin to emerge 4–8 weeks after regions experience local outbreaks of SARS-CoV-2 have identified several potential post-infectious inflammatory syndromes, although not all cases have been associated with proven SARS-CoV-2 infection. The most concerning is the development of multisystem inflammatory syndrome that includes rash and shock, with symptoms overlapping with toxic shock syndrome and atypical Kawasaki disease.[51,88,89] The CDC has proposed classifying these cases as Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2.[90] To date, MIS-C has not been reported in pediatric organ transplant recipients.

Data describing COVID-19 in pediatric SOT are limited. Initial reports from Italy described SARS-CoV-2 detection in 3 of 200 liver transplant recipients, none of whom developed clinical pulmonary disease and all had favorable outcomes.[91] Another report described a 6-month-old infant with biliary atresia whose living donor (mother) tested positive for SARS-CoV-2 2 days after transplant. The infant also tested positive and developed transaminitis and patchy bilateral lung opacities on day 6 after transplant. A liver biopsy was interpreted as ACR, but the child did not respond to augmented immunosuppression and eventually improved with reduced immune suppression. This report raised concerns for possible donor-derived COVID-19 hepatitis although community acquisition would also be possible.[92] A 3 years old more than 2 years after orthotopic heart transplantation developed donor-specific anti-HLA antibodies after a recent viral illness. During therapy for AMR, the patient was coughing and tested positive for SARS-CoV-2 by PCR from a nasal swab. No antiviral therapy or modification in immunosuppression aside from IVIG administration was provided.[93]

Pediatric-specific COVID-19 treatment data are limited. Given the mild course in the vast majority of pediatric patients and the lack of current evidence that disease is more severe in pediatric transplant recipients, supportive care is the recommended

treatment for COVID-19 in these patients. Remdesivir, ideally as part of clinical trial, has been proposed as the preferred agent if antiviral therapy is to be used, Two randomized trials enrolling down to the age of 12 years (NCT04292730, NCT04292899)[94] and two expanded access protocols (NCT04302766 and NCT04323761) are currently available to children <18 years of age in the United States.[94] Anecdotal use of COVID-19 convalescent plasma use in pediatric patients has been reported but further controlled data are needed to assess its efficacy and it is currently, available for children as an open clinical trial (ccpp19.org) or as a single-patient eIND[43] for children considered at high risk of COVID-19 disease progression. There is no current evidence to support use of anti-cytokine/cytokine receptor antibodies in the treatment of COVID-19 in children.

3.8 | Psychological and ethical considerations during the pandemic

There is ample evidence that the COVID-19 pandemic has adversely impacted the psychological health of patients and providers alike. Harm-reduction strategies implemented to attenuate viral transmission—including physical distancing and quarantine—have increased social isolation, loneliness, anxiety, fear, depression, anger, cognitive changes, and posttraumatic stress symptoms. Business closures have further limited opportunities for social engagement and have contributed to severe financial and economic hardship for many families.

The psychological impact for transplant patients may be even more pronounced than that of the general public. Waitlisted patients and transplant recipients may still require some in-person clinic visits, laboratory visits, interventional procedures, and hospitalization during the pandemic, all of which may cause anxiety about potential viral exposure. The potentially higher mortality rate among transplant patients who are COVID+ also may trigger an escalation in anxiety and fear about possible exposure. For transplant candidates, many programs throughout the United States paused or restricted transplant surgeries, creating uncertainty among patients about increased waiting time for transplantation and associated morbidity and risk of mortality on the waiting list. The pandemic also may have altered the social circumstances for waitlisted patients, including changes in caregiving arrangements and increased isolation from traditional support systems. Planned posttransplant support mechanisms may also have been disrupted by physical distancing and travel restrictions. Those with preexisting mental health conditions or substance use disorders may be especially vulnerable to clinical levels of depression or anxiety and relapse to alcohol or drug use.

It is imperative that transplant programs have a process in place to assess the impact of COVID-19 on various domains of a patient's quality of life such as physical, psychological, and financial well-being. Repurposed use of tablets or other devices to enhance communication with patients who lack technology, as well as helping patients learn to effectively use the technology, may be necessary. Nonurgent in-person clinic visits are restricted for many programs during the pandemic, which further distances the patients—and their caregivers—from the resources typically available to them. Periodic telephone or remote video visits with patients and caregivers by transplant social workers, psychologists, and psychiatrists are encouraged to assess the COVID-19 impact on the patient and his/her social support system. Use of specific tools to assess the COVID-specific impact on patients should be considered, including the Epidemic-Pandemic Impacts Inventory (EPII) and the COVID-19 Peritraumatic Distress Index (CPDI). Moreover, telehealth can be utilized to offer individual psychotherapy, virtual support groups for patients and/or caregivers, and connecting transplant patients and caregivers with peer mentors. Rapid and early response to COVID-related stress as well as clear communication from the transplant team about effective risk mitigation strategies may improve the long-term mental health outcomes for transplant patients.

Potential and former living donors also may experience heightened psychological stress in the COVID-19. Some family members and friends of transplant candidates whose living donation evaluation or surgery was postpone due to COVID-19 can be expected to have new ambivalence about donation due to changes in personal circumstances (eg, new caregiving responsibilities), financial stressors caused by the pandemic, anxiety about the risk of viral exposure in a hospital setting and the risk those around them at home, and new concerns about mortality if COVID+ and only one functioning kidney (eg, high rate of mortality among those with COVID and acute kidney injury). Transplant programs, including independent living donor advocates, must assess these new contextual considerations in their evaluation and follow-up contacts with potential and former living donors, respectively.

Finally, it is imperative that individual transplant providers and team dynamics be closely monitored during the COVID-19 pandemic. The impact of COVID-19 on their patients, necessary modifications in clinical practice, temporary pauses in transplant clinics and surgery, higher rates or mortality in transplant recipients with COVID-19, challenging ethical dilemmas in the face of scarce health care resources, and the personal impact of the pandemic on transplant providers make them vulnerable to both short- and long-term mental health sequelae. Ongoing, multi-component psychosocial resources and institutional support are needed.

3.9 | Research priorities

The pandemic creates unique challenges for the population of immunosuppressed transplant patients. These include ensuring equitable access for transplant candidates and recipients in relevant prospective clinical trials. Other questions that must be investigated including how to better manage immunosuppressive therapies. In theory, reducing immunosuppression can improve potential immunity against the virus; however, in the case of SARS-CoV-2 patients,

a significant reduction of immunosuppression could hypothetically exacerbate inflammation and result in aberrant cytokine release. Some papers have been published, but their findings mostly reflect individual experiences all show different approaches in managing immunosuppression.[1,3] Randomized trials that help answer this question are of paramount importance. The number of patients at each center are limited, thus domestic/international collaborations between centers are necessary. Other major questions that need further investigation are related to the role of commonly used immunosuppressive therapies in transplant patients such as steroids, calcineurin inhibitors, and antimetabolites in the disease process.

As of yet, there are no published studies beyond a case series describing the incidence and clinical course of SARS-Cov-2 in transplant recipients. Do transplant recipients who develop SARS-CoV-2 have higher/more prolonged viral detection and infectivity? And do pediatric transplant patients serve as reservoirs for the community spread of SARS-CoV-2? Knowledge of the humoral and cell-mediated immune responses in transplant recipients to infection and future vaccines will also be important. Reactivation of other viruses during COVID infection, such as BK and CMV, require further investigation.

DISCLOSURE

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

DATA AVAILABILITY STATEMENT

There are no data to be shared.

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APPENDIX 1

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APPENDIX 1 (Continued)

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