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REVIEW ARTICLE

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The COVID-19 pandemic: A community approach

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Abstract

An unprecedented global pandemic caused by a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has quickly overwhelmed the health care systems worldwide. While there is an absence of consensus among the community in how to manage solid organ transplant recipients and donors, a platform provided by the American Society of Transplantation online community "Outstanding Questions in Transplantation," hosted a collaborative multicenter, multinational discussions to share knowledge in a rapidly evolving global situation. Here, we present a summary of the discussion in addition to the latest published literature.

KEYWORDS

immune deficiency, immunosuppressant, infection and infectious agents

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1 | INTRODUCTION

A novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the cause of the clinical illness Coronavirus disease 2019 (COVID-19), emerged from its epicenter in Wuhan, China, in December 2019 and has led to a global pandemic.[1] This pandemic has cost thousands of lives and quickly overwhelmed healthcare systems in many countries around the world, putting a halt to our lifestyles and the global economy in an unprecedented manner. Due to the scale of this emergency, the risk of infection by this virus, and the need to allocate resources to the care of COVID-19 positive patients, a similar devastating impact has been observed in transplantation worldwide. Major disruptions on operations pertinent to donors, recipients, as well as transplant professionals led to a significant decrease in the chance to obtain a transplant in a timely fashion and placed the post-transplant follow-up in significant jeopardy.

Our understanding of COVID-19 pathophysiology has grown quickly, but many questions remain unanswered. A large number of clinical trials have been initiated with results that have already helped clinical decision-making in some cases. However, even with this progression, there is still no well-established treatment for this condition. To date, published information regarding the incidence and clinical course of COVID-19 in transplant recipients has primarily been in the form of case reports and case series. While these are valuable, larger multicenter and comparative studies are awaited in order to determine the optimal management of COVID-19 in transplant recipients, who constitute a potentially high-risk population due to their ongoing immunosuppression and higher incidence of comorbidities.[2,3] These uncertainties have fueled anxiety and have ignited an urgent need for further information and discussion.

In July 2017, the Community of Transplant Scientists (COTS) within the American Society of Transplantation (AST) created an online community called "Outstanding Questions in Transplantation," a platform that allows clinicians and scientists to meet and exchange ideas about current challenges in the transplantation field. We launched the SARS-Cov-2 pandemic discussion in March 2020 in response to the increasing number of cases in the United States. It was awe-inspiring to see members from China, Europe, and the US front-lines come together to exchange experiences, frame questions and try to find answers to the unprecedented challenges imposed by the worst pandemic of the last century. To date, the total number of posts on this topic is over 750 with almost 300 unique contributors. We are grateful to all the participants in this lively exchange.

2 | METHODS

In this paper, we have summarized the AST discussion in addition to the latest published literature, dividing it into six major areas of interest: epidemiology, pathophysiology, prevention, logistics, management of immunosuppressive therapies, and treatment. The discussion started March 13, 2020 and continued until the date of this paper's preparation in May 27th. While this discussion was primarily US based, many members from China and Europe participated in the discussion as well. This does not represent an endorsed AST guidelines nor does it constitute a comprehensive evidence-based review.

3 | EPIDEMIOLOGY IN ORGAN TRANSPLANT RECIPIENTS

As of June, 2020 over eight million confirmed cases of COVID-19 have been reported globally with over 445 000 associated deaths.[4] SARS-CoV-2 is known to be transmitted through respiratory droplets[5] and remains viable in aerosols and surfaces,[6] This observation suggests that multiple routes of transmission are possible for this virus. The majority of affected individuals have mild symptoms thus making accurate identifications of the disease very challenging; indeed, individuals infected with SARS-CoV-2 are asymptomatic for a median of 5.1 days and nearly all individuals who develop symptoms do so within a median of 12 days.[7,8] Due to the high rate of asymptomatic or pre-symptomatic infection and limited availability of testing, the true prevalence of COVID-19 is unknown and is likely underestimated significantly based on confirmed cases alone. A population-based study in Iceland[9] found that 13.3% of individuals targeted for testing based on symptoms tested positive for SARS-CoV-2, but so did 0.8% of asymptomatic individuals in the population, with higher rates among males and adults.[9] Early reports indicated that older age and medical comorbidities were more common among documented cases of COVID-19.[10] Risk factors for severe disease among those affected with COVID-19, estimated to be 14% of cases, are still being elucidated. In a cohort of more than 4000 patients in New York City, risk factors for hospitalization included older age, morbid obesity, and heart failure.[11]

At this time, the disease prevalence in organ transplant recipients is unknown. Experience with prior coronavirus outbreaks suggests that transplant recipients may have higher susceptibility to infection, higher risk of severe disease, and prolonged shedding of potentially infectious virus.[12] Transplant recipients may also be at higher risk of secondary infectious complications. Several case series describing COVID-19 in transplant recipients have been published with the largest series from New York City.[3,13,14] In the New York Presbyterian hospital system, 90 solid organ transplant recipients were diagnosed with SARS-CoV-2 infection, with 30% having severe disease. 44 patients were non-kidney transplant recipients (17 lungs, 13 livers, 9 hearts, and 5 dual-organ). Risk factors for severe disease were hypertension and active malignancy. Overall case fatality was 24%, and 22% of patients remained hospitalized at the time of reporting.[14] At Montefiore Medical Center, among a population of 36 kidney transplant recipients hospitalized with COVID-19, there was a 28% mortality rate at 3 weeks.[13]

Additional small series from China, Italy, France, and the US highlight a lower frequency of fever at presentation, some presentations

without typical respiratory symptoms, and a range of clinical severity.[15-26] In several series, mortality appears to correlate with the presence of advanced age and comorbid conditions.[27-31]

The effects of COVID-19 have also exacerbated healthcare disparities to vulnerable groups in the US population. Across the nation, especially in large cities, the majority of patients and the highest mortality have been observed in Blacks and Hispanics mainly due to what is thought to be a lack of "social distancing privilege."[32] This observation holds true in SOT recipients with COVID-19: In the New York city cohort, 29 out of 36 kidney transplant recipient with COVID-19 were black or Hispanic.[13]

The epidemiology of the unprecedented COVID-19 pandemic is unique, and timely dissemination of information concerning this novel virus will be critical to coordinate an appropriate response.

4 | COVID-19 PATHOPHYSIOLOGY

Coronaviruses are spherical virions with a core shell and surface projections. They have large (~30-kb) single-stranded, positive-sense RNA genomes. The surface spike glycoprotein (S protein) on the surface of the virus binds to the receptor angiotensin-converting enzyme 2 (ACE2). ACE2 is expressed in many organs, including the bronchus and lung parenchyma, heart, kidney, and gastrointestinal tract.[33] After binding to the receptor, a nearby host protease cleaves the spike glycoprotein, facilitating virus entry.[33] Endosomal cell entry of SARS-CoV-2 is facilitated by a low pH and pH-dependent endosomal cysteine protease cathepsins. Once inside cells, SARS-CoV-2 exploits the endogenous transcriptional machinery of the host cell to replicate and spread throughout the entire lung.[33]

The pathophysiology of COVID-19 is still poorly understood. Infected cells release mediators and chemokines that rapidly recruit neutrophils. While such neutrophils may limit viral spread, they also secrete cytokines and chemokines that attract further immune cells such as monocytes and T cells, fueling the exaggerated immune responses that may lead to cytokine storm, ARDS, and multi-organ failure.

Complement activation has also been described in SARS-CoV-2-infected patients, a phenomenon possibly implicated in the pathogenesis of acute lung injury and ARDS. Gao et al,[34] identified MBL-associated serine protease-2 (MASP-2) as the target of the N-proteins for SARS-CoV-2. The lung injury induced by other known coronaviruses in mice was attenuated when either the N-protein-binding motif was truncated, the MASP-2: N-protein interaction was pharmacologically blocked, or MASP-2 was knocked out. Preliminary data from patients treated with an anti-complement C5a blocking antibody suggest a potential benefit of complement targeting therapies in COVID-19 patients with severe lung injuries.[34]

Patients with severe COVID-19 have higher plasma levels of IL-6, IL-10, and TNF-α and fewer circulating CD4 and CD8 T cells than individuals with mild disease or healthy controls.[35] Lymphocytopenia may be mediated by TNF-α which can promote T-cell apoptosis. Similarly, the cytokine storm can promote apoptosis or necrosis of T cells, and consequently lead to their reduction.[36] This trend is even stronger in elderly patients. Intriguingly, the most severe COVID-19 cases also have increased percentages of T cells with an exhausted phenotype. However, it is not clear if the T-cell exhaustion is due to the persistence of the virus, the type of inflammation elicited by the virus, or both.[37]

The durability of neutralizing antibody responses against SARS-CoV-2 currently remains unknown. The discussants pointed out that "antibody responses to COVID-19, like other virally mediated pulmonary diseases (including MERS, SARS, and RSV) may reduce viral replication, but also may not reliably prevent infection, and more importantly appear to mediate marked pulmonary inflammation. These observations are critically important, as pulmonary inflammation is the primary mediator of death from these diseases. In fact, the primary reason that vaccines for RSV have failed is that children who received the vaccine, and subsequently acquired RSV, had much higher death risk due to pulmonary inflammation, whereas those children who were not vaccinated had minimal risk of inflammation." Current research investigates whether neutralizing antibodies may preferentially prevent viral replication whereas non-neutralizing antibodies may enhance inflammation and immunopathology, perhaps via immune complex-based activation of innate immune cells. There are all very relevant issues that should be carefully considered in the follow-up of patients who recovered after SARS-CoV-2 infection.

5 | PREVENTION OF VIRAL SPREAD

Prevention of viral spread is a major focus of all medical facilities impacting both patients and healthcare workers (HCW). While viral spread was thought initially to be primarily through contact with an infected individual from the primary infection zone, it has become obvious that there is community spread of SARS-CoV-2 from asymptomatic infected individuals. Hence, most agree that the rules to prevent viral infection in the general population would apply to transplant patients.[5]

5.1 | Inpatient

For inpatient care, more extensive preparation has been recommended including rescheduling elective surgery, shifting urgent inpatient diagnostic and surgical procedures to outpatient settings, limiting visitors to the hospital, and creating surge space to manage known or suspected COVID-19 patients.[5] The modified Traffic Control Bundling (TCB) model is an example of such environmental controls, based on the Taiwan's SARS experience in 2003[38,39] and involves triaging patients outside the hospitals in outdoor screening stations to ensure segregation of patients into 3 zones separated by strict check point stations. "Hot zone" for positive COVID-19 patients, "intermediate zone" for patients under investigation, and "clean zone" for non-COVID-19 patients. Patients triaged to the intermediate or hot zones move along

routes other than those taken by healthcare workers (HCW). Also, HCWs must have gowns, gloves, and eye protection along with N-95 masks upon entering these two zones. As HCWs transition between different zones, they engage in hand disinfection with 75% alcohol and use adequate PPE.[38]

5.2 | Outpatient

Critical to facilities planning is the foresight that transplant patients with potential COVID-19 infection may require immediate care management far from the Transplant Center. As Transplant Centers in high prevalence areas have implemented their emergency care plans, they may be unable to accept patients in transfer or provide acute outpatient management. Separation of immunosuppressed/immunocompromised patients from COVID-19 infected patients on site has been implemented in some facilities that have sufficient space and resources. Moreover, non-COVID-19 urgent care may be required in transplant recipients, again, at a distance from their typical transplant center. Planning for phone triage, telehealth and electronic consultations are important steps for academic medical centers that may be overrun with acutely ill infected patients.

5.3 | Personal protective equipment (PPE)

The utilization of PPE is a critical feature, not only to avoid patient-to-patient transmission, but also transmission to healthcare workers. For known infected patients, Centers for Disease Control and Prevention (CDC) recommendations include eye protection, gowns, gloves, and N95 respirators.[40] Personal powered air-purifying respirators (PAPRs), previously specified by federal standards for high-hazard procedures, are of limited availability and may be implemented in high-risk situations such as bronchoscopy or intubation. Moreover, as data emerges from other endemic locations across the world,[41] it is apparent that there is clear environmental contamination that supports the use of social distancing and other environmental controls. This has implications for patients and healthcare providers outside of healthcare settings: Any provider could potentially be exposed to COVID-19 and act as vectors for disease transmission to the community. Such data support our recommendation for patients and provider to practice "social distancing" and self-isolation if a known exposure occurs.

5.4 | Transplant program logistics

5.4.1 | Transplant clinics and administration

Due to COVID-19 concerns and visitor restrictions to most clinics, most transplant centers have rescheduled in-person visits for stable patients. Initially, the majority of transplant centers canceled outreach clinics, particularly those that required flights. In place of in-person visits, HIPAA compliant telecommunication technologies utilizing electronic medical record systems have allowed for early implementation or expansion of telemedicine programs, thus minimizing the risk of COVID-19 transmission. Many aspects of coordination of patient care, including scheduling and nurse coordinator responsibilities, have been shifted to remote workstations and virtual meetings. Many staff meetings and daily briefings have been converted to telecommunication meetings and webinars. As COVID-19 disease cases have begun to stabilize in many communities, in-person and outreach clinics have begun to re-open. However, telemedicine continues to remain an option for many patients, and centers are better understanding how to fully and efficiently implement these technologies on a more routine basis.

5.4.2 | Living donor transplant

As a general rule, most agree that living donor transplant should not place unnecessary and additional risk to the donor. Early in the outbreak period, The Transplantation Society made the following recommendations[42]:

1. In communities with widespread transmission, temporary suspension of the living donor kidney and liver programs should be considered.
2. Donors should not be utilized if they have fevers or respiratory symptoms, and SARS-CoV-2 should be ruled out.
3. Living donation should not be performed on either the donor or recipient who has returned from places with a high incidence of infection or has been exposed to another individual with confirmed or suspected COVID-19 within 14 days.

It is worth noting that since these recommendations were made, the incidence of COVID-19 has continued to rise throughout the world. In fact, the United States has quickly developed to have the highest number of cases in the world.[43] While COVID-19 testing capacity has increased significantly, the true prevalence and incidence of the SARS-CoV-2 virus is not yet known in the United States. Therefore, considering that kidney/liver living donation is not thought of as lifesaving in the short term, many transplant centers in the United States initially suspended their living donor programs. The rationale behind suspension of living donors programs included: (a) ensure donor and recipient safety by minimizing unnecessary exposure, and (b) minimize the utilization of hospital capacity should a spike in COVID-19 cases begins to challenge resources.

However, as transplant centers and hospital systems have started to understand disease prevalence within their own communities, many have recently re-started their living donor programs. It is recommended to screen the living donor and recipient candidates for SARS-CoV-2 prior to proceeding to the operating room. If negative, a thorough discussion should be initiated with the donor and recipient regarding the risks and benefits of such a procedure with consideration for this still evolving pandemic.

5.4.3 | Deceased donor transplant

Kidney transplantation is not thought to be lifesaving in the short term, so there needs to be consideration for not performing these procedures if hospital resource utilization has been stretched due to an influx of COVID-19 patients. During the initial phases of this pandemic, many programs in the United States were transplanting kidneys in patients who were highly sensitized or where a potential donor has a zero-antigen mismatch. Additionally, many patients received kidneys with a low risk of delayed graft function, as these patients were discharged from the hospital within a few post-operative days. Consideration for switching from lymphocyte depleting agent induction to basiliximab should be given for low-risk patients. Many programs continued to transplant liver, hearts, and lungs unless maximal hospital resource utilization was occurring in those centers where COVID-19 was prevalent.

At the present time, many programs have returned to previous practices of kidney, liver, heart, and lung transplant. Many centers have implemented a COVID-19 screening for all recipients when they are called in for transplantation. We recognize that not all centers have access to rapid screening tests that will result within a few hours of testing. At minimum, we would recommend COVID-19 screening for all potential recipients if they are currently hospitalized at the time of organ offer.

While the true prevalence of disease is still not known, the majority of organ procurement organizations are performing COVID-19 screens on all donors. Recognizing that current COVID-19 screens continue to have a high false-negative rate,[44] most experts recommend caution when proceeding with acceptance of organs when the donor has as follows:

1. Died from respiratory causes of unknown etiology
2. Unexplained and abnormal chest imaging findings, and
3. Had recent contact with individuals with known or suspected COVID-19 infection.

The risk of transmission of the SARS-CoV-2 through solid organ transplantation utilizing tissues of infected donors remains unclear. The presence of intact virions in a specific tissue, detected by electronic microscopy and followed by positive viral culture to confirm replication, would establish infectivity. In contrast, a nucleic acid detection, using real-time polymerase chain reaction (RT-PCR) and immunohistochemistry, would only demonstrate the presence of a viral component in tissue. By consensus, infected lung donors are considered very high risk for transmission given SARS-CoV-2 virus is primarily isolated from the respiratory tract; therefore, it should not be considered for transplantation.[45,46] The use of non-lung tissue from infected donors with the SARS-CoV-2 virus remains controversial. Huang et al detected SARS-CoV-2 RNA in the blood of 15% (6/41) critically ill patients in Wuhan, China, raising the concern for potential bloodstream viral transmission to recipients of infected tissue donors.[36] An autopsy on COVID-19 patient showed hepatocellular, renal, and cardiac damage at several degrees.[47] A case report of a COVID-19 patient in cardiogenic shock and myocarditis required VA-ECMO was notably for the presence of viral particles in the endomyocardial biopsy.[48] In a retrospective study, 6.9% of patients with COVID-19 have positive SARS-CoV-2 RNA in the urine[49]; in another study, 29% of patients (44/153) patients have positive SARS-CoV-2 RNA in the stool.[50]

6 | WELLNESS & RESOURCE UTILIZATION

There are a number of ways that healthcare providers can maintain mental well-being in the face of a pandemic and thus be better equipped to care for infected patients. A key strategy includes having an understanding of Psychological First Aid which is a technique that has been developed to reduce distress in a disaster situation.[51]

The priorities identified in the Psychological First Aid model include: ensuring the safety of individuals affected by disaster followed by connecting these individuals with their families and support networks. Additionally, it is essential to provide a calm presence to combat the impact of panic with an emphasis on helping the afflicted and their providers to maintain their own needs such as sleep, nutrition, and taking breaks and using existing resources to triage those in need of additional services. Thus far, the limited medical literature related to COVID-19 suggests significant stress and post-traumatic stress disorder (PTSD) for those on the frontline of the pandemic,[52] further emphasizing the need for self-care for healthcare providers.

Resilient coping strategies have been identified and likely would mitigate the impact of COVID-related stressors. The following resilient coping strategies have been identified and include: optimism, problem-solving, flexibility, acceptance, providing help to others, exercise, maintaining social support networks, emulating resilient role models, philosophical or spiritual resources, and humor.[53]

6.1 | Medical distancing

Social isolation and uncertainty are likely contributing factors to the anxiety and distress experienced by individuals who are required to social distance to help prevent the spread of the virus.[54] Previous research suggests that those who are quarantined are at increased risk for psychological distress.[55] One study suggested that those who are sheltering at home with their family are not likely to experience marked distress.[56] Providing additional support to staff members who are isolated or quarantined is warranted including strategies such as emphasizing the importance of staying connected with their primary support network, maintaining a sense of meaning and purpose through work to help others either possibly using telemedicine or other outreach efforts and monitoring for symptoms suggestive of post-traumatic stress disorder.

Support through electronic forums such as the "Outstanding Questions in Transplantation" on the American Society of Transplantation website likely serve as an important link for individuals

experiencing the highly stressful combination of caring for very ill patients, being concerned for the well-being of fellow coworkers and potentially facing exposure to the virus themselves. Ultimately, utilizing existing resources including employee assistance programs, physician well-being teams, wellness programs or peer support may enhance staff resilience in the setting of prolonged stress from the pandemic.[51]

7 | MANAGEMENT OF ANTIREJECTION THERAPY

Solid organ transplant recipients may be at a particularly higher risk of developing critical Covid-19-related complications due to chronic immunosuppression as well as other comorbidities. There is an absence of consensus in how to adjust immunosuppression in Covid-19 kidney transplant recipients and how they should be treated.[57] Reduction or withdrawal of calcineurin inhibitors, mycophenolate mofetil (MMF), mycophenolic acid (MPA), azathioprine, or mTOR-inhibitors was considered in patients with Covid-19. However, complete withdrawal of immunosuppression or significant reduction of immunosuppression could hypothetically exacerbate inflammation in the absence of anti-inflammatory agents. In contrast, continuation of immunosuppressive treatment could decrease in mounting an antibody response to virus. It is not clear at what point during progression of clinical deterioration that immunosuppression should be minimized or stopped, and when and if initiation of anti-inflammatory agents improve clinical outcomes in transplant recipients with COVID-19. It is not clear if there is a role for the commonly used immunosuppressive therapies in transplant patients such as steroids, calcineurin inhibitors, and antimetabolites in preventing or treating cytokine storm.

(Italian experience?) in 20 kidney transplant recipients with COVID-19 pneumonia documented a fast progression in more than 75% of their patients with 25% mortality.[2] At admission, all had immunosuppression withdrawn and were started on methylprednisolone 16 mg/d, antiviral therapy, and hydroxychloroquine. Montefiore Medical Center experienced a high mortality (28%) in kidney transplant recipients and had imaging findings of viral pneumonia in 96% of hospitalized patients. From these patients, 39% required mechanical ventilation and 21% required renal replacement therapy.[13] Immunosuppressive management included discontinuation of mycophenolate in 86% of the patients and tacrolimus in 21% of the patients with a severe clinical picture. A survey responded by 26 transplant centers in USA reported that 92% stopped anti-metabolite, 15% stopped and 27% decreased dosages of calcineurin inhibitor.[58]

Mycophenolic acid was shown to inhibit MERS-CoV papain-like protease, an important viral target for viral maturation.[59] However, there is no clinical study investigated in vivo effects of MMF/MPA in patients with coronavirus infection. Two other important points need to be considered for continuation of MMF/MPA. First, leukopenia, lymphopenia is common in kidney transplant patients with COVID-19 and seen up to 80%,[13] which makes difficult to continue MMF/MPA without dose adjustment. Second, seroconversion rates to influenza vaccination were especially low in those on MMF of 2 g or greater daily (44.4% vs 71.4%), which potentially indicates a difficulty to mount an antibody response to COVID-19 with high dose MMF.[60]

Many concerns were raised on the hub regarding the need for clinical trials to identify the best practices to manage immunosuppressive therapies in our population. While reducing immunosuppression can improve potential immunity against the virus; a significant reduction could potentially exacerbate hyperinflammation and result in aberrant cytokine release.

8 | TREATMENT

No therapeutic agents or vaccines have been FDA approved to treat or prevent COVID-19 to date.[61] Early in the pandemic, the "Outstanding Questions in Transplantation" served as a valuable resource to discuss early treatment literature (largely not yet peer-reviewed at that point) and share how other centers in the United States and internationally were using drugs with reported in vitro activity against SARS-CoV-2 and anti-inflammatory agents in transplant recipients with COVID-19. Now, several months in to the pandemic, there is a rapidly expanding body of peer-reviewed literature assessing, novel antiviral agents and older drugs with in vitro activity against SARS-CoV-2 and other coronaviruses. In addition, many clinical trials of potential therapies are in progress. The three categories of drugs or interventions being tested are as follows: (a) antivirals to restrain viral proliferation or cell injury, (b) convalescent plasma, and (c) immunomodulatory agents targeting the uncontrolled inflammatory response against the virus. Because of the urgency of the COVID-19 pandemic, and need to share promising results as rapidly as possible, some early non-randomized studies on therapeutic outcomes have been published in preliminary and/or non–peer-reviewed form, which should serve as a caveat when interpreting results of those studies. Despite the rapid proliferation of literature about COVID-19 therapies, few publications have looked at treatment specifically in transplant recipients. Here, we provide an overview of some of the potential COVID-19 therapies debated in the "Outstanding Questions in Transplantation" forum based on review of important studies performed in all patients types, with discussion of treatment in transplant patients where available.

8.1 | Antiviral therapy

8.1.1 | Lopinavir-ritonavir

Lopinavir-ritonavir is a protease inhibitor approved to treat HIV.[62] Despite initial promising results from uncontrolled studies, a Chinese clinical trial (ChiC-TR2000029308) in 199 patients with COVID-19 pneumonia showed that treatment with lopinavir-ritonavir with standard supportive care compared to standard care alone was not associated with a significant difference in the time to clinical improvement or mortality.[62] A post hoc subgroup analysis showed a

trend in favor of lopinavir-ritonavir in patients treated within 12 days after the onset of symptoms, so it is possible that it might be more effective if given early in the course of illness. Lopinavir-ritonavir was associated with more gastrointestinal adverse events. Notably, protease inhibitors in general, and ritonavir in particular, inhibit liver cytochrome activity and thus have several major drug interactions including with calcineurin inhibitors, mammalian targets of rapamycin inhibitors and other medications which complicates their use and has caused significant toxicity in solid organ transplant recipients in several reported cases.[63,64]

Whether early lopinavir-ritonavir treatment in Covid-19 could improve viral clearance is unknown.[65] Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 recommend the use of lopinavir-ritonavir only in the setting of clinical trials.[66]

8.1.2 | Chloroquine and hydroxychloroquine

SARS-CoV-2 needs an endosomal acid pH for processing and internalization.[67] In vitro data indicate that the antimalarial drug chloroquine exerts antiviral effects by increasing endosomal pH and abrogating virus-endosome fusion. Hydroxychloroquine is an oral derivative of chloroquine that has fewer side effects. Besides its antiviral activity, hydroxychloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo.[68] Early clinical interest and significant debate among OQT respondents was spurred by two non-randomized French studies that suggested potential efficacy of hydroxychloroquine, in rapid viral clearance, possibly in combination with azithromycin.[69,70] Several recent peer-reviewed observational and large registry studies have suggested chloroquine and hydroxychloroquine may have no impact and may even increase mortality. An observational study of hydroxychloroquine in 1446 patients cared for at a large medical center in New York City that used propensity score matching found no association between hydroxychloroquine use and the composite risk of death or intubation.[71] Furthermore, in another recent multicenter retrospective cohort study of 1438 patients hospitalized in New York state with COVID-19, there was no difference in in-hospital mortality among patients on no treatment compared to those on hydroxychloroquine, hydroxychloroquine with azithromycin, or azithromycin alone.[72] A recent randomized controlled trial in 821 asymptomatic participants at high-risk or moderate-risk exposure to Covid-19 showed no benefit of hydroxychloroquine in preventing disease.[73]

Overall, these data do not support the use of these treatments in COVID-19 patients, including organ recipients.

8.1.3 | Remdesivir

Remdesivir is an adenosine analogue with a broad-spectrum antiviral effect as an inhibitor of viral RNA polymerases.[74] It incorporates into nascent viral RNA chains and results in pre-mature termination.[74] Remdesivir inhibits SARS-CoV-2 in vitro[68] Grein et al[75] reported promising clinical outcomes among 53 patients with severe illness due to COVID-19, more than half of whom required mechanical ventilation, treated with one or more doses of remdesivir for compassionate use. Even more compelling are the preliminary results of a randomized blinded trial of remdesivir for the treatment of COVID-19 in 1063 patients with evidence of lower respiratory tract infection.[76] Patients treated with remdesivir had a shortened recovery time of 11 days compared to 15 in the placebo group. Numerically, there were fewer deaths by day 14 among those treated with remdesivir (7.1% vs 11.9%) but it did not meet statistical significance. Serious adverse events were similar between the two groups. Remdesivir is currently being studied in other clinical trials, and results from those randomized trials and the final results of the trial above, should shed more light on its efficacy.

8.1.4 | Convalescent plasma

The use of convalescent plasma was recommended as an empirical treatment during outbreaks of Ebola virus in 2014, and a protocol for treatment of Middle East respiratory syndrome coronavirus with convalescent plasma.

Shen et al administered convalescent plasma transfusions to 5 patients with COVID-19 and ARDS. The donors had recovered from SARS-CoV-2 infection and had been asymptomatic for at least 10 days, with documented anti-SARS-CoV-2 antibodies. In all five patients, the neutralizing antibody titers significantly increased after plasma transfusion, the viral load declined, and the clinical conditions improved.[77] Duan et al[78] reported the clinical outcomes amount 10 patients with severe illness due to COVID-19 treated with convalescent plasma. Notable changes reported within days after administration included improved oxygen saturations and inflammatory markers. A recent comprehensive Cochrane review of convalescent plasma for COVID-19 that included 8 different studies, none of which were controlled, was unable to draw conclusions about the effect of convalescent plasma in COVID-19 but pointed out that there are currently 48 active studies of this therapy, 22 of which are randomized.[79] Most recently, Liu et al[80] reported the Mount Sinai experience with convalescent plasma in 39 COVID-19 patients, compared with retrospectively matched controls, and reported that convalescent plasma improved survival in non-intubated patients (hazard ratio 0.19 (95% CI: 0.05~0.72); $P = .015$) but not in intubated patients.

AST members raised questions in the discussion about convalescent plasma, such as whether or not it might contain high titers of anti-HLA antibodies, and also what effects standard unselected IVIg might have on COVID-19. Currently, available intravenous immunoglobulin would not yet contain specific antibodies against SARS-CoV-2, but might reduce SARS-CoV-2-induced inflammatory responses by blocking FcR activation to. Such treatment may also be combined with systemic anti-inflammatory drugs or corticosteroids.

A single-center, randomized, open-label, controlled trial, will evaluate the efficacy and safety of IVIG therapy in patients with pneumonia caused by SARS-CoV-2 (NCT04261426).

Based on the reports of potential utility of convalescent plasma, multiple efforts are underway to identify neutralizing antibodies within this plasma, and to develop monoclonal antibodies with specific anti-SARS-CoV-2 activity. Future clinical trials are expected.

8.2 | Anti-inflammatory therapies

8.2.1 | Steroids

The use of high dose corticosteroids remains unclear and subject of debate in the setting of COVID-19. The rationale behind using corticosteroids is to decrease inflammatory response in the lungs. However, it also has the potential to delay viral clearance and increase risk of secondary bacterial infections. The use of steroids is not recommended by the World Health Organization outside of clinical trials, because of potential inhibition of viral clearance and prolongation of the duration of viremia.[81] Stockman et al[82] analyzed the treatment during the SARS outbreak of 2002-2003, but, despite an extensive literature reporting on SARS treatments, it was not possible to determine whether treatments benefited patients. A retrospective analysis of 201 patients with COVID-19 pneumonia showed that corticosteroid use was associated with lower mortality and lower ARDS, but the authors did not adjust for confounding factors and there could be a biased in this observational study.[10] A recent press release from the RECOVERY trial showed that dexamethasone significantly reduced mortality in 2104 COVID-19 patients compared with 4321 controls on standard therapy.[83] These data are likely to change the practice on COVID-19 patients, including transplant recipients.

8.2.2 | Anti-IL-6/IL-6R therapies

Patients with severe COVID-19 pneumonia show increased levels of circulating IL-6. An early manuscript detailing outcomes in 21 patients with severe pneumonia due to COVID-19 treated with tocilizumab, a recombinant humanized monoclonal antibody against the human IL-6 receptor, that reported improvements in fever, oxygen requirements, and inflammatory markers sparked considerable interest in the use of drugs that block the effects of IL-6.[84] Tocilizumab is used for rheumatoid arthritis, and also used in treatment of cytokine-release syndrome after administration of chimeric antigen-receptor (CAR) T cells in leukemia, a scenario with similarities to the inflammatory phase of COVID-19. Xu et al reported decreases in fever, oxygen requirement, and C-reactive protein, and increases in absolute lymphocytes counts in 20 patients who received tocilizumab for severe COVID-19.[85] There are currently multiple clinical trials testing the efficacy of anti-IL6 (siltuximab and clazakizumab) and anti-IL6 receptor antibodies (tocilizumab and sarilumab) in patients with COVID-19 pneumonia.

Effects of the IL-6 and IL-6 receptor inhibitors in transplant recipients with COVID-19 are not yet fully known, although case reports have suggested excellent responses in some patients. Several OQT respondents shared preliminary data and clinical impressions that effects were mixed, with benefits mainly in patients who were hypoxemic but were not yet requiring mechanical ventilation. Subsequently, some of these respondents, and other colleagues from centers with larger numbers of SOT recipients, have published their data on clinical outcomes and therapeutics in these patients. Pereira et al, from two centers in New York City, reported on 90 SOT recipients with COVID-19, of whom 91% received hydroxychloroquine, 66% azithromycin, 3% remdesivir, 21% tocilizumab, and 24% bolus steroids.[86] Sixteen patients died (18% overall, 24% of hospitalized, 52% of ICU). The 16 patients who received tocilizumab included 6 with moderate and 8 with severe disease, but the authors commented that no firm conclusions could be drawn about the effects of any one therapeutic modality.[14] Akalin et al[13] reported on 36 kidney transplant recipients admitted to Montefiore Medical Center, of whom two received tocilizumab.

The multicenter registry established by Kates et al, which provided weekly summaries in the OQT forum, included approximately 9% who received tocilizumab; data analysis is in progress to ascertain the effects of this therapy and the optimal timing, if given. There is are also ongoing discussions about the optimal anti-infective monitoring and prophylaxis in the aftermath of tocilizumab administration, or other similar therapies, given the potential for secondary infections.

The Janus kinase (JAK) inhibitors ruxolitinib (NCT04362137, others) and baracitinib (NCT04373044, others) are currently under study for their potential to reduce cytokine release in the inflammatory phase of COVID-19. Baracitinib may also have antiviral effects (NCT04390464).[87] Other immunomodulatory therapies that have been used off-label or are in clinical trials for COVID-19, for protection against pulmonary injury and inflammatory progression, include the Bruton tyrosine kinase inhibitors ibrutinib[88] and acalabrutinib (NCT04380688) complement inhibitors eculizumab (NCT04346797) and ravulizumab (NCT04390464), and the CCR5 inhibitor leronlimab (NCT04343651).[13]

This is only a partial list, and there are many other agents of potential interest. Further reports on the effects of these or other immunomodulatory therapies on transplant recipients will be valuable, as it is not possible to generalize from effects in the overall population with COVID-19.

8.3 | RAS inhibitors

Angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, is a membrane-bound aminopeptidase that cleaves angiotensin I and angiotensin II into the angiotensin-(1-9) and angiotensin-(1-7) peptides.[67] This, together with higher disease severity in individuals with diabetes or cardiovascular disease who are often in

therapy with renin-angiotensin system (RAS) inhibitors, raised concerns about the use of these drugs that may alter ACE2 expression.

In response to some media sources and health systems that have recently called for the discontinuation of RAS inhibitors, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have emphasized the lack of any evidence to support discontinuation of RAS inhibitors in the context of the pandemic COVID-19 outbreak.[89-91]

Therefore, RAS inhibitor withdrawal both prophylactically and in the context of suspected COVID-19 is not advised and may be harmful in certain high-risk patients with known or suspected COVID-19. There is a single-center randomized clinical trial in progress, to assess whether administration of prazosin might prevent cytokine storm in COVID-19 (NCT04365257).

In all new candidate therapies for COVID-19, whether antiviral therapies, passive immunity, immunomodulatory therapies, or future vaccine trials, the OQT respondents generally agreed that it will be extremely important to assess the risks and benefits in transplant recipients, given special considerations in their infection risk and complex immunologic status.

8.4 | What is needed to reopen transplantation programs?

With the pressing need of growing wait lists for recipients even during the pandemic, and ongoing urgent needs for hearts, lungs, and livers, transplant programs have been considering this question since the onset of closures of their medical centers. However, the Centers for Medicare and Medicaid Services had designated transplantation as a Tier 3B surgical procedure (akin to trauma and urgent vascular procedures) and as such, an essential service. Hence, while transplantation fell to all-time lows during April 2020, transplantation did not come to a halt entirely. As already noted, while living donation closed down to barely perceptible volumes, even these programs have begun reopening. Deceased donor transplantation has been ongoing, while not at a robust volume as in pre-COVID19 days. Clearly, the variability of disease prevalence is contributing to varied approaches to program functions, not unlike that seen in the general public. This question was recently addressed by the consortium of transplant professional groups across the world[92] and two issues emerged: personnel safety and patient safety.

In regards to programmatic safety, transplant practices have changed throughout the pandemic.[58] In a survey study of nearly 80% of transplant centers in the United States, programs offered concerns regarding resources during the pandemic with regards to safety including ventilators, OR and anesthesia staff availability, ICU beds, PPE, and sufficient patient testing. Additional recommendations were voiced by ASTS including avoiding OR presence during intubation for the transplant team, and recognition that other contributing factors such as aerosolized spread via laparoscopic procedures, and electrocautery highlighted in a recent webinar of transplant experts.[93] Patient testing continues to be paramount to management, with recognized limitations to current testing tools and limited data regarding RNA persistence and viral replication post-initial infection.[94] Hence, a positive PCR test may remain positive for several days post-initial symptomatic infection, and centers need to determine their risk threshold to proceed, and how frequently to test post-operatively. Testing of potential recipients pre-transplant appears to be a standard practice in all solid organ transplants.[95] A second aspect is organs for donation. For living donations, some transplant programs continued throughout the pandemic with a low point of 11 during the week of April 5, 2020[96] and currently on the upswing. Program activity is focal and regional, in areas where the pandemic has been less severe and based on risk acceptance thresholds as recently demonstrated.[97] Programs depend on the ability to access testing for living donors and recipients prior to transplantation with guidelines for this pre-donation testing for both living and deceased donors.[98] Furthermore, for deceased donor organs, OPOs have had to adapt to fluctuating organ availability and limiting retrieval team access in and out of endemic hotspots.[99] All potential donors are being tested for COVID-19 using Broncho-alveolar lavage (BAL), endotracheal aspirate, and nasal swabs with good accuracy of results.[100] The current practice is to not utilize donors that are SARS-COV2 positive due to concerns of transmission risk although this has recently been debated.[45,101]

Additionally, transplant center's need to assure follow-up plans utilizing robust Telehealth interactions have been implemented universally. With the implementation of the Coronavirus Preparedness and Response Supplemental Appropriations Act, as signed into law by the President on March 6, 2020, certain Medicare telehealth payment requirements during the Public Health Emergency (PHE) have been waived to allow beneficiaries in all areas of the country to receive telehealth services. Barriers in implementation for transplantation have been recently outlined.[102] Additionally, frequent lab monitoring may include home visits or local lab collection and several commercial entities have added this service to their portfolios to include immune monitoring with the overarching goal to limit patient access into the medical center and prevent unnecessary exposure.[60]

8.5 | How to inform patients

Informed consent allows recipients and their family members to fully consider the risks and benefits of accepting a donor organ and was noted to be an area of concern in the discussions by the group. A reasonable approach that would allow for a balanced view of both the risks and benefits of organ donation in the area of COVID 19 was articulated during a discussion about restarting programs. The following suggestions were proposed to provide transparency for the recipients and their families including: ensuring the donor tested negative, discussing the chances of a false positive test for the donor, ensuring that the donor had no symptoms suggestive of COVID, weighing the risk of undetected infections against the risk of waiting longer for a donor organ, acknowledging that the medical community never has perfect knowledge of all risks or the

magnitude of known risks, and ensuring that the staff taking care of patients in the ICU wore PPE and were appropriately trained to minimize the risk of transmission. These suggestions demonstrate the need for sufficient time with recipients and family members for thorough and thoughtful conversations to answer questions and address their concerns while recognizing the limits of knowledge in this rapidly changing era.

9 | CONCLUSIONS

We are grateful to the AST members who provided guidance and participated in the discussions and to AJT for publishing the highlights of this initiative. The above summary reflects vigorous discussions on COVID-19-related topics among many AST members, within the email framework of "Outstanding Questions in Transplantation," and does not constitute a guideline or a systematic review of evidence. It is likely that recommendations will change, and that formal guidelines will be created in the future, as more evidence from randomized trials and other clinical experience emerges. However, this does illustrate the value of ongoing collaborative multicenter, multinational discussions in sharing knowledge in a rapidly evolving global situation.

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CONFLICTS OF INTEREST

None.

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