Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Impact of COVID-19 in solid organ transplant recipients

Lara Danziger-Isakov | Emily A. Blumberg | Oriol Manuel | Martina Sester

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exploded onto the world stage in early 2020. The impact on solid organ transplantation (SOT) has been profound affecting potential donors, candidates, and recipients. Importantly, decreased donations and the pressure of limited resources placed on health care by the pandemic also disrupted transplant systems. We address the impact of COVID-19 on organ transplantation globally and review current understanding of the epidemiology, outcomes, diagnosis, and treatment of COVID-19 in SOT recipients.

KEYWORDS
antibiotic: antiviral, COVID-19, health services and outcomes research viewpoint, infectious disease, United infection and infectious agents - viral, immunosuppression / immune modulation, organ procurement, organ transplantation in general

1 | SARS-COV-2 INFECTION, IMMUNITY, AND PATHOGENESIS

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). While infection with SARS-CoV-2 is frequently asymptomatic or mild, clinical manifestations can also be serious. Risk factors for serious disease and mortality in the general population include older age, obesity, and comorbidities affecting the lung or the heart. Disease severity may be influenced by the viral inoculum, dissemination, pre-existing immunity toward other coronaviruses, individual immunocompetence, and other host factors.

In the general population, infection is followed by the induction of innate inflammatory responses and of SARS-CoV-2-specific humoral and cellular immunity including CD4 and CD8 T cells. The magnitude of specific immunity may be directly related to viral load, dissemination to the lower respiratory tract, and/or disease severity. In addition, SARS-CoV-2-specific T cells in patients with severe disease have a restricted functionality and higher expression levels of co-inhibitory receptors, which also extended to T cells in general. Together this suggests that adaptive immunity is readily induced and contributes to viral control in the majority of infected individuals. However, in some patients, a cytokine storm is triggered that mediates severe lung inflammation and widespread systemic pathology. High levels of specific adaptive immunity and the hyperinflammatory syndrome observed in severe disease emphasize the need for contraction processes to counteract excess immunopathology in the lungs.

In solid organ transplant (SOT) recipients, the extent of immunosuppression correlates with the severity of diverse infectious diseases, which led to the initial prediction that SOT recipients may be more susceptible to severe COVID-19. Indeed, the risk of mortality in transplant recipients seems higher than in the general population. However, this has not been universally noted.
Early after infection, strong immunosuppression may adversely affect sufficient induction of specific immunity, which may account for insufficient control of viral load and frequently observed prolonged detection of viral RNA after disease onset. In contrast, in later periods of the disease, immunosuppressive drugs may be beneficial in suppressing proinflammatory processes and supporting functional inactivation and contraction of cellular immunity. Thus, modulation of immunosuppression may be harmful or beneficial depending on the clinical stage of the infection in SOT. The time course for viral replication, infectivity, and induction of adaptive immunity in immunocompetent patients and potential alterations in SOT recipients, and implications for therapeutic management is outlined in Figure 1.

2 | THE IMPACT OF COVID-19 ON TRANSPLANTATION

COVID-19 had immediate impact on transplant activity as the infection became more widespread throughout the world. Initial reports from the Italian epicenter revealed a 25% decline in deceased donation nationally with a more pronounced decline in northern Italy where the rates of COVID-19 were highest. During the height of the first wave of the pandemic in Spain, there was nearly an eightfold decrease in transplant activity. France, the Netherlands, and the United Kingdom (UK) also experienced substantial declines with lower transplant rates driven by 50–90% decrease in deceased donation during the peak COVID-19 months. Review of data from the United States’ United Network of Organ Sharing (UNOS) comparing monthly transplants in January and February 2020 with those performed in April 2020 demonstrated a 35.9% decrease in organs transplanted.

Several themes emerged from all reports. The impact on specific programs exposed notable regional variation, reflecting in part local COVID-19 rates, but also individualized approaches to resource allocation and prioritization. The impact on organ transplantation also varied with respect to organ type with preferential deferral of kidney transplant candidates who were stable on renal replacement therapy and/or had lower immunologic barriers to transplantation. However, the majority of reports also noted a decline in transplantation in all organ types. Living donor programs were generally curtailed or suspended in many sites. Reasons for the decline in donations were diverse and explained by changes at multiple levels in the transplant process, although the impact of individual policies remains uncertain at this time. An overall decline was driven by a decrease in available ICU beds for maintaining donors due to use for treatment of critically ill COVID-19 patients. The demographics of the available donors shifted with a 5% decline in trauma death donors, 35% increase in donor death by substance abuse, and a decreased willingness to use donors with circulatory deaths in whom post-operative transplant recovery would be anticipated to be prolonged. Donor screening practices varied but in

![FIGURE 1 Time course of SARS-CoV-2 infection and development of COVID-19. After infection with SARS-CoV-2, individuals may transmit the virus 1–2 days prior to and approximately 8 days after the onset of clinical symptoms (red curve). SARS-CoV-2 RNA as determined by PCR (orange curve) is detectable for longer periods of time. Infection is followed by the induction of SARS-CoV-2-specific CD4 and CD8 T cells (blue curve) that contribute to the control of viral replication. In addition, a hyperreactive immune response contributes to immunopathology associated with COVID-19. As outlined by stippled curves, PCR positivity after infection may be prolonged in transplant recipients, with potential implications for prolonged infectivity. In addition, induction of specific immunity may be less pronounced given immunosuppressive drug therapy. Implications for therapeutic management are indicated. This includes antiviral drugs or convalescent plasma together with reduction in immunosuppression in the early period of infection to ensure control of viral replication, and immunomodulatory or anti-inflammatory treatment regimens associated with restoring or intensified immunosuppression in the later stages of infection to counteract immunopathology.](image-url)
As the COVID-19 pandemic developed, the impact on transplant recipients began to emerge with reports initially from China, then Italy and Spain.\(^{57-70}\) The prevalence of infection in SOT during the first wave of the pandemic varied geographically. In New York City, 22 (5.5\%) of approximately 400 heart transplant recipients followed at a single center acquired COVID-19.\(^{71}\) Similarly, 5\% (66/1216) kidney transplant recipients in a French surveillance program were identified with COVID-19.\(^{72}\) A study from 12 kidney transplant centers following 9845 patients reported 144 (1.5\%) kidney transplant recipients hospitalized with COVID-19 over a 9-week period.\(^{73}\) The largest and most comprehensive evaluation to date interrogated the UK transplant registry over a 4 months period from February to May 2020.\(^{74}\) Positive testing for SARS-CoV-2 was identified in 3.8\% (197/5184) of waitlisted patients and 1.3\% (597/46789) of transplant recipients.

The average age of SOT recipients with COVID-19 ranged from 50 to 71 years and presented an average of 3–6 years posttransplant.\(^{77,71,75-80}\) According to several reports, Blacks and Hispanics were disproportionately affected with US centers reporting 39–100\% of SOT admissions with COVID-19 involving Black patients and one center noting that 15\% of COVID-19 infected patients were Hispanic.\(^{81-83}\) These differences were seen globally with 40\% Hispanic and 25\% Black in cases from the TANGO collaborative of centers in Spain, Italy, and the United States.\(^{73}\) More extensive investigation is underway to address the underpinning causes of these differences which may be related not only to local penetrance of SARS-CoV-2 and prevention measures but also to significant concerns of systemic bias related to socioeconomic status and race.

The presentation of SOT recipients with COVID-19 appears similar to the general population. Fever (61–83\%), cough (45–75\%), and diarrhea (22–57\%) were the most common symptoms reported.\(^{14-16,71,75,79,80,83-88}\) Abnormalities in chest imaging occurred frequently; cohorts of SOT recipients in New York City reported abnormal chest radiographs in 96–100\%.\(^{83,84}\) As testing availability increased and understanding of the spectrum of symptoms improved, the proportion of SOT recipients with abnormal initial chest radiographs decreased to 50–75\%.\(^{75,89}\) In the limited number of patients with initial chest CT, all were abnormal with half (4/8) showing infiltrates in more than 50\% of the lung.\(^{89}\)

Hospitalization, morbidity, and mortality from COVID-19 ranged broadly across populations and countries. Reported hospitalization rates ranged from 32 to 78\% in most studies that included outpatients.\(^{14-17}\) However, reporting bias certainly occurred, especially in large cohorts with voluntary reporting of cases and limited testing availability early in the pandemic for non-hospitalized patients. In recent international cohorts, 78–89\% of identified patients were hospitalized which is higher than in the general public, although this also may reflect reporting or testing bias of differential health care utilization for transplant patients.\(^{77,90}\) Once hospitalized, rates of transition to the intensive care unit ranged from 8.6\% in the Netherlands to
### Table 1: General recommendations by selected transplantation societies for transplant center guidance

| Society                                      | Decision to transplant                                                                 | Deceased donation                                                                                       | Living Donation                                                                                     | Transplant Candidates                                                                                                                                 |
|----------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| American Society of Transplantation⁵²        | Balance local COVID−19 epidemiology, resource availability (including of health care staff) with need for transplant. Temporary suspension of elective living donor transplantation or non-urgent deceased donor transplants may be considered based on local concerns. | Epidemiologic screen and ≥1 respiratory tract NAT (BAL for lungs) within 72 hours of donation.          | Exclude living donors with COVID−19 (symptoms and/or NAT positive). Epidemiologic and NAT screening (respiratory tract only) within 72 hours of donation. Pre donation self-quarantine 14 days. | Defer transplantation for active SARS-CoV−2 infection. NAT negative at time of transplant; disease-free interval not specified. |
| American Society of Transplant Surgeons⁵³    | Consider curtailing transplantation services when 20–25% of hospital resources are committed to COVID−19 care or there is a very rapid increase in COVID−19 population numbers. Assumes availability of appropriate PPE and measures for HCW screening, social distancing and COVID−19 free areas in transplant center. | Epidemiology screen including local donor hospital environment/ exposures by NAT (BAL recommended). Chest CT findings of ground glass should be assessed in view of COVID−19 risk. Local team organ recovery preferred Strict adherence to use of PPE for all phases of recovery (including travel) | Exclude living donors who are NAT positive. NAT screening 2 days prior to donation. Negative CXR Asymptomatic donors should self-isolate for a minimum of 7 days, preferably 7–14 days. Special informed consent form of COVID−19 risk appreciation. | Transplant surgery/ immunosuppression is not advised in symptomatic or asymptomatic infected individuals with COVID−19 |
| The Transplantation Society⁵⁴               | All transplant-related teams should develop plans for: HCW absences due to illness, identification of remote workforce, messaging for patients with contacts in case of illness, risk mitigation, screening of sick patients. | Epidemiologic and NAT screening of all donors. Defer use of donors with COVID−19 unless 14 days since symptom onset and ideally two negative NAT for SARS-CoV−2. | Epidemiologic and NAT screening of all donors. Defer use of donors with COVID−19 unless 14 days since symptom onset and ideally two negative NAT for SARS-CoV−2. | Discussion of risk benefit of transplantation with candidate during the ongoing pandemic. Defer transplantation of infected patients until 10–14 days since symptom onset, resolution of symptoms and two negative NAT tests separated by 24 hours. |
| International Society of Heart and Lung Transplantation⁵⁵ | Decisions regarding transplantation made locally based on rate of SARS-CoV−2 infection in the community and availability of health care resources, unless otherwise directed by regional or national authorities. Regularly re-evaluate policy and consider individual patient risk benefit as well as local resource issues. Transplant cessation not recommended unless dictated by local circumstances. | Defer donors with active infection. Consider donors with former COVID−19 if two negative NAT 24–48 hours apart if complete clinical recovery and at least 28 days from symptom onset. | Not applicable | Defer transplantation for NAT positive candidates and those with consistent symptoms (regardless of NAT). If history of symptomatic COVID−19, defer transplantation until two negative NAT tests separated by 24–48 hours following full resolution of illness. If history of asymptomatic COVID−19, 14 days must have elapsed since diagnosis and must have two negative NAT tests 24–48 hours apart. |

Abbreviations: NAT, Nucleic acid test; BAL, Bronchoalveolar lavage; HCW, health care worker; PPE, personal protective equipment.
Intubation and non-invasive ventilation ranged broadly from 8 to 60% in smaller cohorts; however, the largest cohorts reported 30%–39% non-invasive ventilation or intubation. Pre-existing comorbidities associated with disease, morbidity, and mortality in the general population have been frequently reported in SOT recipients with COVID-19, potentially impacting the high rates of hospitalization and severe disease. At least one comorbidity was recorded in 18 of 26 (69%) heart transplant recipients from Italy and in 443 of 482 (92%) SOT recipients in a large multi-national cohort. Hypertension (9%–94%), diabetes mellitus (41%–69%), and chronic kidney disease (37%–89%) were most common. Incidence of superinfection occurred at a higher rate in SOT recipients compared to controls (50% vs. 15.5%).

Mortality ranged from 9 to 46% with most in the 18%–30% range depending on the cohort and circumstances. All-cause mortality during the study period of the UK registry reached 26% for SOT recipients and 10% for those on the waitlist, although local utilization decisions related to resource availability may have impacted these numbers. The largest cohort to date including 482 SOT recipients from more than 50 transplant centers reported 20.5% mortality, and two compilations of cases found 18%–19% mortality overall. In a UK database analyzing 10926 COVID-19 related deaths, SOT recipients had a hazard ratio of 3.53 [95% CI 2.77–4.49] for death as compared to the general population. Mortality rates may be biased by hospitalization. In a small study among 35 SOT recipients that was restricted to hospitalized patients, morbidity and mortality was similarly high compared to hospitalized non-transplant patients (48% vs. 40%). Intubation portended poor outcome with 40%–100% of ventilated patients dying in small cohorts. Interestingly, according to a series of 26 pediatric SOT recipients, children did not suffer significant morbidity, with none requiring oxygen support and all recovering within 7 days, mirroring the less severe course described in immunocompetent pediatric patients.

Many studies have addressed risk factors for mortality with older age, underlying cardiovascular or lung disease, increased inflammatory markers and lymphopenia, and pre-existing frailty. More recently, the presence of SARS-CoV-2 viral RNAemia was reported as increased risk for both disease severity and mortality in kidney transplant recipients, while viral load from swabs of the upper respiratory tract was not related to disease severity. Differences in the intensity of immunosuppression did not appear to affect mortality aside from a report in heart transplant recipients where discontinuation of immunosuppression was associated with mortality.

Persistence of symptoms including fatigue and dyspnea for more than 60 days has been reported in a non-transplant population from northern Italy; however, data on long-term patient and graft outcomes among transplant recipients are currently lacking.

### 4 | SARS-COV-2 TESTING IN TRANSPLANT RECIPIENTS

Direct SARS-CoV-2 assays and information on infectivity in the setting of organ transplantation are essential to identify infected patients, to discontinue isolation and to screen potential donors, candidates and recipients. Specimen sources include nasopharyngeal, nasal or throat swabs, and bronchoalveolar lavage (BAL) with polymerase chain reaction (PCR) platforms or antigen testing employed. With early testing platforms, negative initial testing did not eliminate the possibility of infection. In one cohort, as many as 8% of SOT recipients with initial negative SARS-CoV-2 PCR had subsequent positive testing.

Evidence from the general population including viral culture assays suggests that PCR positivity from nasopharyngeal swabs declines within 3 weeks, whereas infectivity already decreases within 8 days after symptom onset, respectively. Longer PCR positivity may apply for BAL or sputum samples. Interestingly, prolonged duration of positive PCRs from nasopharyngeal swabs was reported fairly early in the pandemic in SOT recipients. A positive PCR was discovered in a heart transplant recipient 35 days after onset of symptoms, and in a kidney transplant recipient 63 days after onset despite positive serologic response on day 47. Other cases in kidney and lung recipients have confirmed prolonged PCR positivity at more than 30 days post-symptom onset, with up to 25% of cases in a French cohort. Additional data regarding prolonged PCR positivity and potential transmission of replication-competent SARS-CoV-2 from SOT recipients are needed to address issues around infection prevention and isolation practices, as correlation between PCR positivity and infectivity in SOT recipients remains uncertain. Rapid antigen tests with acceptable performance characteristics are now becoming available; this may improve screening time in some settings.

Indirect assays such as SARS-CoV-2-specific serology and cellular immunity have been evaluated in limited circumstances in SOT recipients. Serologic response to SARS-CoV-2 has been reported in cases and series of kidney and lung recipients. In a small study among seven patients admitted to the hospital, all developed IgG against the nucleocapsid protein of SARS-CoV-2 between 5 and 27 days after the onset of symptoms. In 116 samples from 35 kidney transplant recipients either IgM or IgG against SARS-CoV-2 recombinant nucleocapsid and spike antigens were positive in all survivors and samples more than 14 days after symptom onset, and sustained through day 59.
suggest that SARS-CoV-2-specific CD4 and CD8 T cells are induced shortly after infection, contributing to viral control,\textsuperscript{6,10} which also was observed in a case report of a renal-pancreas recipient\textsuperscript{113} and a small series of kidney transplant recipients.\textsuperscript{114} However, no data are available on the stability of cellular immunity in the long term. As new data continue to emerge, understanding the role of serology and specific T cells in defining prior infection or in predicting outcome, recovery, and protection from reinfection will be essential.

5 | TREATMENT STRATEGIES INCLUDING IMMUNOSUPPRESSION-RELATED MODIFICATIONS

Given the high mortality associated with COVID-19 in hospitalized patients, and in particular for SOT recipients, several antiviral or immunomodulatory drugs have been given as compassionate use for therapy of COVID-19 since the beginning of the pandemic (Figure 2).

5.1 | Antiviral therapy

Antiviral drugs for SARS-CoV-2 were initially chosen based on observational data obtained during the SARS-CoV-1 and MERS-CoV outbreaks,\textsuperscript{115,116} or in vitro activity against SARS-CoV-2.\textsuperscript{117,118} The first series of cases of SOT recipients infected with SARS-CoV-2 showed that a significant percentage of patients were treated with hydroxychloroquine (ranging from 25% to 90%) and/or lopinavir/ritonavir (3%-50%).\textsuperscript{117,119,84,89} None of these drugs have shown efficacy in clinical trials and are currently not recommended.\textsuperscript{119,120}

The most promising antiviral drug tested for COVID-19 is remdesivir.\textsuperscript{121} Remdesivir is an inhibitor of the viral RNA-dependent RNA polymerase with in vitro activity against SARS-CoV-2. EC\textsubscript{50} of remdesivir in in vitro models against MERS-CoV and SARS-CoV-2 was 0.09 µM and 0.77 µM, respectively.\textsuperscript{117,122} A double-blind placebo controlled trial including more than 1000 patients given 10 days of remdesivir treatment showed a significant reduction of time to recovery from 15 days in the placebo group to 10 days in the remdesivir group (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49).\textsuperscript{123} However, reduction of mortality was not statistically significant. The beneficial effect of remdesivir was predominantly seen in patients needing oxygen but was not apparent in those on mechanical ventilation or on ECMO. Of note, no significant toxicity has been observed in trials using remdesivir, or in case reports specifically in SOT recipients.\textsuperscript{66} Drug-drug interaction with immunosuppression has not been described and is not anticipated. More recently, the Solidarity trial, a large international WHO-sponsored trial compared 2700 patients receiving remdesivir with the local standard of care with preprint preliminary results available\textsuperscript{124} and noted no effect of remdesivir on mortality (10.9% vs. 11.1% with standard of care). A

![FIGURE 2](image-url)  
FIGURE 2: Timeline of SARS-CoV-2 identification, selected announcements, and therapeutic milestones related with COVID-19. The yellow line shows the cumulative number of cases worldwide (source: John Hopkins Coronavirus research Center). COVID-19, coronavirus disease 19; FDA, Food and Drug Administration; HCQ, hydroxychloroquine; PEP, postexposure prophylaxis; RCTs, randomized clinical trials; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant; WHO, World Health Organization.
meta-analysis of all existent interventional data on remdesivir was included in the Solarity publication and showed a risk ratio (RR) of death with remdesivir of 0.91 (95% CI 0.79–1.05, \( p = .20 \)), being 0.80 (95% CI 0.63–1.01) in patients without mechanical ventilation. Thus it appears that remdesivir should be given early after the infection onset to reduce viral load and avoid the development of the cytokine storm phase in patients who may have risk factors for a worse outcome, a category that includes SOT recipients.\(^{121}\)

Administration of convalescent plasma (CP) of infected patients has been approved for emergency use in the US based on observational data that includes an acceptable safety profile.\(^{125}\) Although the first randomized clinical trial was underpowered and failed to show clear clinical benefit across all patients, it appears that CP is superior in reducing viral load and time to clinical improvement when administered early in the disease course rather than after the onset of life-threatening disease.\(^{126}\) A more recent trial compared CP with standard of care in non-transplant patients (\( n = 464 \)); no reduction in progression to severe disease or mortality was noted with CP,\(^{127}\) perhaps due to the presence of similar neutralizing antibody titers in both study arms. Thus, it seems that sufficient antibody titers may be essential to confer clinical efficacy. Data on the use of CP in SOT recipients are limited to case reports.\(^{128,129}\) Apart from antibody treatment with CP, several highly active monoclonal antibodies against SARS-CoV-2 are currently under evaluation.\(^{130,131}\) An anti-spike neutralizing antibody named LY-CoV555 has shown a reduction in SARS-CoV-2 viral loads in outpatients with COVID-19 in a phase II trial.\(^{132}\)

### 5.2 Immunomodulatory therapy

The unique clinical course of COVID-19, with initial viral clearance followed by the development of a second clinical phase characterized by the release of inflammatory cytokines and coagulation factors, prompted the introduction of anti-inflammatory and immunomodulatory drugs for reducing the deleterious effects of the immune reaction to SARS-CoV-2. Given that interleukin-6 (IL-6) was elevated in patients with COVID-19, several studies assessed whether inhibiting IL-6 by blocking the IL-6 receptor with tocilizumab could have beneficial effects. In an uncontrolled study including 20 non-transplant patients with mild to moderate COVID-19 in China, a reduction in inflammatory parameters (including CRP) and clinical symptoms (fever, dyspnea) was observed after administration of tocilizumab; none of the patients died.\(^{133,134}\) However, none of three recent randomized controlled trials having compared tocilizumab with standard of care and/or placebo in the general population has shown a reduction of mortality.\(^{135–137}\) In SOT recipients, a Spanish cohort of kidney transplant recipients receiving tocilizumab for COVID-19 reported an overall mortality of 32%. However, tocilizumab was given to patients with more severe disease, so that the effect of tocilizumab on mortality cannot be assessed.\(^{138}\) A case-control study involving 117 SOT recipients from New York showed that tocilizumab was not associated with a reduction of mortality.\(^{139}\)

Steroids have been evaluated for treatment of COVID-19. The Recovery trial including more than 11000 patients in several arms, compared the efficacy of dexamethasone 6 mg once daily with the standard of care alone for treatment of COVID-19.\(^{140}\) Patients on dexamethasone had an overall 17% decrease in mortality (rate ratio, 0.83; 95% CI, 0.75–0.93). This effect was particularly seen in patients who received oxygen (rate ratio, 0.82; 95% CI, 0.72–0.94) and those on mechanical ventilation (rate ratio, 0.64; 95% CI, 0.51–0.81), but not in patients not receiving oxygen (rate ratio, 1.19; 95% CI, 0.91–1.55).\(^{140}\) A recent meta-analysis of seven randomized controlled trials confirmed the beneficial effect of steroids on reducing COVID-19 mortality (OR, 0.66; 95% CI, 0.53–0.82).\(^{141}\) These data indicate that steroids should be used in all patients with COVID-19 who need oxygen and/or mechanical ventilation. In SOT recipients, increasing the dose of prednisone or adding dexamethasone as part of the modulation of immunosuppressive therapy may be recommended in case of advanced disease.

Clinical trials are currently testing other immunomodulatory drugs such as Janus kinase inhibitors (baricitinib),\(^{142}\) IL-1 blockers (anakinra),\(^{143}\) and anti-C5 inhibitors (eculizumab) among many others.\(^{144}\)

### 5.3 Management of immunosuppression and risk of rejection

Modification of the immunosuppressive regimen is part of the therapeutic prescription in SOT recipients who develop a viral infection. Transplant physicians usually suspend antimetabolites and/or reduce calcineurin inhibitors dosing in case of severe viral infection, such as CMV disease or influenza, in an attempt to restore antiviral immunity and consequently increase viral clearance.\(^{145}\) However, in patients with COVID-19 modulation of immunosuppression is a more pressing challenge, as most of the severe manifestations of COVID-19 are consequence of the imbalanced host response consisting of low expression of interferons and high expression of pro-inflammatory cytokines.\(^{146}\) Theoretically, maintenance of immunosuppression with inhibition of T cell immunity may have beneficial effects on reducing this inflammatory response.\(^{147}\) However, the potential benefit of immunosuppression in patients with COVID-19 is counterbalanced by the high number of comorbidities present in SOT recipients.\(^{75,84}\) Experience in cohorts of SOT recipients showed that calcineurin inhibitors were held in 18%-29% of patients and antimetabolites were held in 66%-88% of patients during the clinical course of COVID-19.\(^{17,84,95}\) It has been hypothesized that belatacept, by blocking the costimulatory signal, may prevent a severe clinical course of COVID-19; however, reports of both mild and severe cases of COVID-19 in SOT patients receiving belatacept have been published.\(^{63,148}\) Despite the lack of strong evidence on optimal immunosuppression management in SOT recipients,\(^{149,150}\) a stepwise reduction of immunosuppression according to the severity of the clinical presentation may be appropriate. In asymptomatic patients and patients not requiring hospitalization, modification of
immunosuppression may be deferred. In patients needing low-flow oxygen, a dose reduction of the metabolite and/or reduction of calcineurin inhibitors or mTOR inhibitor levels may be necessary, especially in patients receiving other immunomodulatory drugs. In more severe cases, including those requiring ICU admission with mechanical ventilation and/or ECMO, some centers have applied a more significant immunosuppression reduction strategy, with temporary discontinuation of all immunosuppressive drugs, except steroids. This strategy needs to be balanced with a potential increased risk for the development of acute rejection and/or graft loss, particularly in life-saving transplants. However, other experts propose continuation of calcineurin inhibitors (particularly cyclosporine) during advanced disease to control the inflammatory phase. 149

Another matter of concern is a potential increase in acute rejection rates due to administration of less potent immunosuppressive regimens for transplant recipients transplanted during the pandemic. Data from the Scientific Registry of Transplant Recipients showed a reduction in the use of ATG induction after March 2020 as compared to previous months, despite the fact that ATG was associated with a reduction in acute rejection rates and had no effect on mortality. 151 In addition, suboptimal posttransplant follow-up with concerns in drug compliance during lockdown may additionally result in increased rejection risk. 152 However, few studies have assessed the rates of acute rejection associated with COVID-19 itself or due to modulation of immunosuppression during infection. While a significant rate of AKI has been reported in kidney transplant recipients, the actual incidence of acute rejection has not been systematically reported, mostly due to the absence of allograft biopsies performed. 153 In a multicenter cohort involving 482 patients, only seven episodes of rejection were observed (six cellular and one humoral rejection). 17 Other studies in kidney and heart recipients with COVID-19 did not report diagnosis of rejections, despite reduction or withholding of immunosuppression in significant proportions of patients. 15,94 Increased doses of steroids administered during COVID-19 may partially explain the observed low rates of acute rejection. In any case, the complex management of immunosuppression during the course of infection should be discussed in a multidisciplinary approach by transplant physicians, ICU doctors, and transplant infectious diseases specialists.

6 | CONSIDERATIONS IN THE PERI-TRANSPLANT PERIOD

SARS-CoV-2 infections in the early period after transplantation appear to have a higher morbidity and mortality as compared to infections in long-term transplant recipients, which may be directly related to the intense immunosuppressive drug regimens including induction therapies. Among 36 patients, 2 of 10 patients who died were early transplant recipients with T cell depleting agents received within the previous 5 weeks. 83 Similarly, two of five recent liver transplant patients died after nosocomial infection diagnosed 9 and 36 days after transplantation. 154 Finally, among three kidney and one liver transplant recipients who contracted SARS-CoV-2 infection from an asymptomatic surgeon between 7 and 10 days after transplantation, one kidney recipient died after rapid clinical deterioration. 155 Peri-transplant infection may also adversely affect graft outcome as suggested by a kidney transplant recipient with SARS-CoV-2 infection 24 days after transplantation who developed acute respiratory distress syndrome (ARDS) and AKI with induction of donor specific antibodies. 101 Based on the recognition of this higher risk, multiple transplant organizations have released recommendations regarding protecting newly transplanted patients from acquiring SARS-CoV-2. 41,45 Potential reasons for COVID-19 in the peri-transplant period include asymptomatic infection of the recipient at or around the time of transplantation, donor-derived infections, community acquired infections by family members or social contacts, or nosocomial transmission by health care workers and/ or patients in health care facilities. 154-156 Screening of recipients and donors to exclude infection at the time of surgery seems mandatory as any type of surgery in a SARS-CoV-2 infected patient has been associated with significant postoperative pulmonary complications and high mortality. A European study involving 1128 patients with confirmed SARS-CoV-2 infection within 7 days before or 30 days after surgery were found to have a 30-day mortality of 23.8%, which increased to 38.0% among the 52.2% of patients with pulmonary complications. 157 Thus, apart from significant comorbidities among transplant recipients and intense immunosuppression in the early transplant period, transplant surgery itself might impact the outcome of recipients with asymptomatic or donor-derived infection. Although proven donor-derived infections have not yet been reported, this may be more likely to occur in lung transplant recipients due to a high burden of viable virus in the lung allograft. Given detection of viral RNA in other organs such as the gastrointestinal tract, 158,159 liver 160 or kidney, 161 transmission could also occur. The lack of donor-derived infections should not be considered as a low likelihood for transmission, but success of prevention policies including anamnesis to identify high-risk contacts and donor screening. 41,45,162 Continued vigilance and testing will not only protect potential recipients but also health care and transplant procurement teams and prevent viral transmission between institutions during procurement. Transplantation of infected candidates and utilization of organs from donors with COVID-19 are currently only recommended after resolution of clinical symptoms and negative PCR testing. Initial reports of transplant recipients with resolved SARS-CoV-2 infection have shown favorable outcome. 163 Case reports of inadvertent transplantation of asymptomatic SARS-CoV-2 positive donors without transmission to the recipient 164 may indicate a potential use of PCR positive donors for life-saving procedure, especially when more is known about the correlation between PCR positivity and infectivity. 108-110 After transplantation, strict adherence to careful infection prevention strategies and physical distancing are important preventive measures to prevent SARS-CoV-2 acquisition. 41,45,162 In SOT recipients who have contracted SARS-CoV-2, longer periods of PCR positivity 18-21 may require a longer duration of isolation and testing to reduce the risk for transmission.
7 | TRANSPLANTATION AS TREATMENT FOR SEVERE COVID-19

Given concerns for irreversible organ damage especially to the lungs from COVID-19, there has been increasing interest in transplantation for COVID-19 induced end-stage lung disease. First cases of lung transplantation in patients with COVID-19 have been reported in China and in Austria. In China, five lung transplantsations were reported in PCR negative patients; one patient died 1 day after surgery. An Austrian team reported successful lung transplantation of a 44-year-old woman. Her PCR was still positive but non-infectivity was confirmed by negative culture. Two additional cases who had developed end-stage pulmonary fibrosis have been transplanted in the United States Careful definition of clinical indications and long-term results are needed to more safely delineate when to consider transplantation as a treatment option for end-stage lung disease.

8 | CONCLUSIONS

SARS-CoV-2 and the resulting COVID-19 pandemic have had a profound impact on the world and SOT in particular. Our current understanding has benefitted from the immense productivity and collaboration of scientists and clinicians around the globe, specifically in describing the epidemiology and impact of the virus on transplantation. As data develop regarding the pathogenesis of the virus and its immunologic impact, emerging therapies will require investigation specifically in SOT recipients, a population in whom the balance between viral control, immune activation, and preservation of graft function requires careful navigation. Global efforts in the development and clinical evaluation of SARS-CoV-2 vaccines have proceeded at an unprecedented pace. Several types of vaccines including attenuated or inactivated whole viruses, protein or peptide vaccines, viral vectors or viral nucleic acids are being explored with promising safety and immunogenicity profiles, and large phase 3 studies are currently being performed worldwide. Apart from reluctance toward the use of attenuated whole viruses after transplantation, all vaccine types should hold promise for application in SOT recipients. Nevertheless, data on safety and immunogenicity are currently lacking for SOT, and the potential benefits of a SARS-CoV-2 vaccine in effectively reducing the burden of disease will need to be specifically evaluated in the transplant population. In the meantime, passive immunization with convalescent plasma with high neutralizing titers or with monoclonal antibodies may serve as a temporary intervention, especially early in infection. Challenges remain during the ongoing pandemic not only for transplant infrastructure related to resource availability but also from knowledge gaps in potential donor transmission and candidate optimization.

ACKNOWLEDGMENTS

The authors thank Allan Kirk and Sandy Feng for the opportunity to provide this review.

DISCLOSURE

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

AUTHOR CONTRIBUTIONS

L.D.-I., E.B., M.S., and O.M. contributed equally to the development and writing of this manuscript. All authors approved the final version of the manuscript.

ORCID

Lara Danziger-Isakov https://orcid.org/0000-0002-5691-5221
Emily A. Blumberg https://orcid.org/0000-0002-5193-6170
Oriol Manuel https://orcid.org/0000-0001-7607-0943
Martina Sester https://orcid.org/0000-0001-5482-0002

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
3. Grifoni A, Weiskopf D, Ramirez S, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell. 2020;181(7):1489-1501 e1415.
4. Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell. 2020;183(1):158-168 e114.
5. Weiskopf D, Schmitz KS, Raadsen MP, et al. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. Sci Immunol. 2020;5(48).
6. Schub D, Klemis V, Schneiter S, et al. High levels of SARS-CoV-2-specific T cells with restricted functionality in severe courses of COVID-19. JCI Insight. 2020;5(20).
7. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020;370(6515).
8. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020;370(6515).
9. Hou YJ, Okuda K, Edwards CE, et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. Cell. 2020;182(2):429-446 e414.
10. Braun J, Loyal L, Frentsch M, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020;587(7833):270-274.
11. Zheng HY, Zhang M, Yang CX, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. Cell Mol Immunol. 2020;17(5):541-543.
12. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-374.
13. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357(25):2601-2614.
14. Becchetti C, Zambelli MF, Pasulo L, et al. COVID-19 in an international European liver transplant recipient cohort. Gut. 2020;69(10):1832-1840.
15. Feldlin M, Softeland JM, Magnusson J, et al. Initial report from a swedish high-volume transplant center after the first wave of the COVID-19 pandemic. Transplantation. 2020.
16. Husain SA, Dube G, Morris H, et al. Early outcomes of outpatient management of kidney transplant recipients with coronavirus disease 2019. Clin J Am Soc Nephrol. 2020;15(8):1174-1178.

17. Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: A multi-center cohort study. Clin Infect Dis. 2020.

18. Man Z, Jing Z, Huibo S, Bin L, Fanjun Z. Viral shedding prolongation in a kidney transplant patient with COVID-19 pneumonia. Am J Transplant. 2020;20(9):2626-2627.

19. Decker A, Welzel M, Laubner K, et al. Prolonged SARS-CoV-2 shedding and mild course of COVID-19 in a patient after recent heart transplantation. Am J Transplant. 2020.

20. Benotmane I, Gautier-Vargas G, Wendling MJ, et al. In-depth virological assessment of kidney transplant recipients with COVID-19. Am J Transplant. 2020.

21. Fung M, Chiu CY, DeVoe C, et al. Clinical outcomes and serologic response in solid organ transplant recipients with COVID-19: A case series from the United States. Am J Transplant. 2020.

22. Angelico R, Trapani S, Manzia TM, Lombardini L, Tisone G, Cardillo M. The COVID-19 outbreak in Italy: Initial implications for organ transplantation programs. Am J Transplant. 2020;20(7):1780-1784.

23. Dominguez-Gil B, Coll E, Fernandez-Ruiz M, et al. COVID-19 in Spain: Transplantation in the midst of the pandemic. Am J Transplant. 2020;20(9):2593-2598.

24. Gumber L, Gumber A. COVID-19 and ‘lockdown’ in organ transplantation. Transpl Immunol. 2020;61:101304.

25. de Vries API, Alwayn IPJ, Hoek RAS, et al. Immediate impact of COVID-19 on transplant activity in the Netherlands. Transpl Int. 2020;33(8):969-970.

26. Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Immediate impact of COVID-19 on solid organ transplantation during the COVID-19 pandemic. Lancet. 2020;395(10237):e95-e96.

27. Cholankeril G, Podboy A, Alshuwaykh OS, et al. Early impact of COVID-19 on solid organ transplantation in the United States. Transplantation. 2020;104(11):2221-2224.

28. UNOS.COVID-19 and solid organ transplant. 2020. https://unos.org/covid/.

29. Arnol M, Smrkolj T, Avsec D, Gadzijev A, Knezevic I. An increase in kidney transplantation procedures from deceased donors during the COVID-19 epidemic in Slovenia. Transpl Int. 2020.

30. Agopian V, Verna E, Goldberg D. Changes in liver transplant center practice in response to coronavirus disease 2019: Unmasking dramatic center-level variability. Liver Transpl. 2020;26(8):1052-1055.

31. Eurotransplant. Statistics report library. 2020. https://statistics.eurotransplant.org/index.php?search_type=donors&search_organ=&search_region=by+country&search_period=2020&search_characteristic=&search_text. Accessed September 27, 2020.

32. Boyarsky BJ, Po-Yu Chiang T, Werbel WA, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. Am J Transplant. 2020;20(7):1809-1818.

33. Vistoli F, Furian L, Maggiore U, et al. COVID-19 and kidney transplantation: an Italian Survey and Consensus. J Nephrol. 2020;33(4):667-680.

34. Ahmed O, Brockmeier D, Lee K, Chapman WC, Doyle MBM. Organ donation during the COVID-19 pandemic. Am J Transplant. 2020.

35. Lentine KL, Vest LS, Schnitzler MA, et al. Survey of US living kidney donation and transplantation programs in the COVID-19 era. Kidney Int Rep. 2020;5(11):1894-1905.

36. Strauss AT, Cartier D, Gunning BA, et al. Impact of the COVID-19 pandemic on commercial airlines in the United States and implications for the kidney transplant community. Am J Transplant. 2020.

37. Division of Nephrology CUVCoP. Disaster response to the COVID-19 pandemic for patients with kidney disease in new york city. J Am Soc Nephrol. 2020;31(7):1371-1379.

38. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020;7(10):e737-e745.

39. Craig-Schapiro R, Salinas T, Lubetzky M, et al. COVID-19 outcomes in patients waitlisted for kidney transplantation and kidney transplant recipients. Am J Transplant. 2020.

40. Aghemo A, Masarone M, Montagnese S, et al. Assessing the impact of COVID-19 on the management of patients with liver diseases: A national survey by the Italian association for the study of the Liver. Dig Liver Dis. 2020;52(9):937-941.

41. Kumar D, Manuel O, Natori Y, et al. COVID-19: A global transplant perspective on successfully navigating a pandemic. Am J Transplant. 2020;20(7):1773-1779.

42. Chung SJ, Tan EK, Kee T, et al. Practical considerations for solid organ transplantation during the COVID-19 global outbreak: The experience from singapore. Transplant Direct. 2020;6(6):e554.

43. Lauterio A, De Carls R, Belli L, Fumagalli R, De Carls L. How to guarantee liver transplantation in the north of Italy during the COVID-19 pandemic: A sound transplant protection strategy. Transpl Int. 2020;33(8):969-970.

44. Lembach H, Hann A, McKay SC, et al. Resuming liver transplantation amid the COVID-19 pandemic. Lancet Gastroenterol Hepatol. 2020;5(8):725-726.

45. Ritschel PV, Neevermann N, Wiering L, et al. Solid organ transplantation programs facing lack of empiric evidence in the COVID-19 pandemic: A By-proxy Society Recommendation Consensus approach. Am J Transplant. 2020;20(7):1826-1836.

46. Wang Y, Yang H, Liu H, Huher LH, Deng S. Strategies to halt 2019 novel coronavirus (SARS-CoV-2) spread for organ transplantation programs at the Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital. China. Am J Transplant. 2020;20(7):1837-1839.

47. Recommendations and Guidance for Organ Donor Testing. 2020.

48. Chew CA, Iyer SG, Kow AWC, et al. An international multicenter study of protocols for liver transplantation during a pandemic: A case for quadrupartite equipoise. J Hepatol. 2020;73(4):873-881.

49. McGregor TB, Sener A, Yetzer K, Gillrie C, Parasekvas S. The impact of COVID-19 on the Canadian Kidney Paired Donation program: an opportunity for universal implementation of kidney shipping. Can J Surg. 2020;63(5):E451-E453.

50. Organ Retrieval for Transplantation in the COVID-19 Era. 2020. https://asts.org/covid/

51. Danziger-Isakov E et al. Organ donation during the COVID-19 pandemic. Vox Sang. 2020;119(4):282-284.

52. American Society of Transplantation. https://www.myast.org/covid-19-information. Accessed November 15, 2020.

53. American Society of Transplant Surgeons. https://asts.org/advocacy/covid-19-resources/asts-covid-19-strike-force/asts-covid-19-strike-force-organ-retrieval-guidance#.X6l7T2aB5aR. Accessed September 27, 2020.

54. Saigal S, Gupta S, Sudhindran S, et al. Liver transplantation and COVID-19 (Coronavirus) infection: guidelines of the liver transplant Society of India (LTSI). Hepatol Int. 2020;14(4):429-431.

55. American Society of Transplantation. https://www.myast.org/covid-19-information. Accessed November 15, 2020.

56. American Society of Transplant Surgeons. https://asts.org/advocacy/covid-19-resources/asts-covid-19-strike-force/re-engag-ing-organ-transplantation-in-the-covid-19-era#.X29pqBS5k2w. Accessed November 15, 2020.

57. The Transplantation Society. Guidance on coronavirus disease 2019 (covid-19) for transplant clinicians. https://tts.org/index.php?option=com_content&view=article&id=749&Itemid=140. Accessed November 15, 2020.

58. The International Society for Heart and Lung Transplantation. https://ishlt.org/ishlt/media/documents/SARS-CoV-2_Guidance-for-Cardiiothoracic-Transplant-and-VAD-centers.pdf. Accessed November 15, 2020.

59. Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant. 2020;20(7):1859-1863.
71. Guillen E, Pireno GJ, Revuelta, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? *Am J Transplant.* 2020;20(7):1875-1878.

72. Gandolfi I, Delsante M, Fiaccadori E, et al. COVID-19 in kidney transplant recipients. *Am J Transplant.* 2020;20(7):1941-1943.

73. Bussalone E, De Maria A, Russo R, Paolotti E. Immunosuppressive therapy maintenance in a kidney transplant recipient with SARS-CoV-2 pneumonia: A case report. *Am J Transplant.* 2020;20(7):1922-1924.

74. Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI. Insight.* 2020;5(10).

75. Huang JF, Zheng KI, George J, et al. Fatal outcome in a liver transplant recipient with COVID-19. *Am J Transplant.* 2020;20(7):1907-1910.

76. Liu B, Wang Y, Zhao Y, Shi H, Zeng F, Chen Z. Successful treatment of severe COVID-19 pneumonia in a liver transplant recipient. *Am J Transplant.* 2020;20(7):1891-1895.

77. Marx D, Moulin B, Fafi-Kremer S, et al. First case of COVID-19 in a kidney transplant recipient treated with belatacept. *Am J Transplant.* 2020;20(7):1944-1946.

78. Ning L, Liu L, Li W, et al. Novel coronavirus (SARS-CoV-2) infection in a renal transplant recipient: Case report. *Am J Transplant.* 2020;20(7):1864-1868.

79. Seminari E, Colaneri M, Sambo M, et al. SARS-CoV-2 infection in a renal-transplanted patient: A case report. *Am J Transplant.* 2020;20(7):1882-1884.

80. Hsu JJ, Gaynor P, Kamath M, et al. COVID-19 in a high-risk dual heart and kidney transplant recipient. *Am J Transplant.* 2020;20(7):1911-1915.

81. Mathies D, Rauschning D, Wagner U, et al. A case of SARS-CoV-2 pneumonia with successful antiviral therapy in a 77-year-old man with a heart transplant. *Am J Transplant.* 2020;20(7):1925-1929.

82. Keller BC, Le A, Sobhanie M, et al. Early COVID-19 infection after lung transplantation. *Am J Transplant.* 2020;20(7):2923-2927.

83. Cozzi E, Faccioli E, Marinello S, et al. COVID-19 pneumonia in lung transplant recipients: Report of 2 cases. *Am J Transplant.* 2020;20(10):2933-2937.

84. Kates OS, Fisher CE, Stankiewicz-Karita HC, et al. Earliest cases of coronavirus disease 2019 (COVID-19) identified in solid organ transplant recipients in the United States. *Am J Transplant.* 2020;20(7):1885-1890.

85. Singhvi A, Barghash M, Lala A, et al. Challenges in heart transplantation during COVID-19: A single-center experience. *J Heart Lung Transplant.* 2020;39(9):894-903.

86. Elias M, Plevani D, Randoux C, et al. COVID-19 infection in kidney transplant recipients: Disease incidence and clinical outcomes. *J Am Soc Nephrol.* 2020;31(10):2413-2423.

87. Cravedi P, Suraj SM, Azzi Y, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant consortium. *Am J Transplant.* 2020.

88. Ravanand R, Callaghan CJ, Mumford L, et al. SARS-CoV-2 infection and early mortality of wait-listed and solid organ transplant recipients in England: a national cohort study. *Am J Transplant.* 2020.

89. Fernández-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients: A single-center case series from Spain. *Am J Transplant.* 2020;20(7):1849-1858.

90. Nair V, Jandovitz N, Hirsch JS, et al. COVID-19 in kidney transplant recipients. *Am J Transplant.* 2020;20(7):1819-1825.

91. Favà A, Cucchiari D, Montero N, et al. Clinical characteristics and risk factors for severe COVID-19 in hospitalized kidney transplant recipients: A multicentric cohort study. *Am J Transplant.* 2020;20(11):3030-3041.

92. Travi G, Rossotti R, Merli M, et al. Clinical outcome in solid organ transplant recipients with COVID-19: A single-center experience. *Am J Transplant.* 2020;20(9):2628-2629.

93. Tschopp J, L’Huillier AG, Mombleni M, et al. First experience of SARS-CoV-2 infections in solid organ transplant recipients in the Swiss Transplant Cohort Study. *Am J Transplant.* 2020;20(10):2876-2882.

94. Yi SG, Rogers AW, Sahara A, et al. Early experience with COVID-19 and solid organ transplantation at a US high-volume transplant center. *Transplantation.* 2020;104(11):2208-2214.

95. Ketcham SW, Adie SK, Mallett A, et al. Coronavirus Disease-2019 in heart transplant recipients in southeastern Michigan: A case series. *J Card Fail.* 2020;26(6):457-461.

96. Sharma P, Chen V, Fung CM, et al. COVID-19 outcomes among solid organ transplant recipients: A case-control study. *Transplantation.* 2020.

97. Akinlin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med.* 2020;382(25):2475-2477.

98. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant.* 2020;20(7):1800-1808.

99. Aversa M, Benvenuto L, Anderson M, et al. COVID-19 in lung transplant recipients: A single center case series from New York City. *Am J Transplant.* 2020.

100. Chaudhry ZS, Williams JD, Vahia A, et al. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: A case-control study. *Am J Transplant.* 2020.

101. Moosavi S, Mashhadiaha A, Motazedian N, Hashemazar, A, Hoveidaei AH, Bolignano D. COVID-19 clinical manifestations and treatment strategies among solid-organ recipients: a systematic review of cases. *Transpl Infect Dis.* 2020:e13427.

102. Imam A, Abukhalaf SA, Imam R, Abu-Gazala S, Merhav H, Khalilieh A. Kidney transplantation in the times of COVID-19 - a literature review. *Ann Transplant.* 2020;25:e292575.

103. Bossini N, Alberici F, Delbarba E, et al. Kidney transplant patients with SARS-CoV-2 infection: The Brescia Renal COVID task force experience. *Am J Transplant.* 2020.

104. Coll E, Fernandez-Ruiz M, Sanchez-Alvarez JE, et al. COVID-19 in transplant recipients: The Spanish experience. *Am J Transplant.* 2020.

105. Hoek RAS, Manintveld OC, Betjes MGH, et al. COVID-19 in solid organ transplant recipients: a single-center experience. *Transpl Int.* 2020.

106. Belli LS, Duvoux C, Karam V, et al. COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry. *Lancet Gastroenterol Hepatol.* 2020;5(8):724-725.

107. Marcault C, Fodil S, Dupont T, Darmon M, Azoulay E. Solid organ transplant recipients during COVID-19 pandemic. *Am J Transplant.* 2020;20(10):2960-2961.

108. Iacovoni A, Boffini M, Pidello S, et al. A case series of novel coronavirus infection in heart transplantation from 2 centers in the pandemic area in the North of Italy. *J Heart Lung Transplant.* 2020;39(10):1081-1088.

109. Caillard S, Anglicheau D, Matignon M, et al. Solid organ transplant recipients during COVID-19: A French perspective. *Kidney Int.* 2020.

110. Molnar MZ, Bhalla A, Azhar A, et al. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. *Am J Transplant.* 2020.

111. Russell MR, Halnon NJ, Alejos JC, Salem MM, Readon LC. COVID-19 in a pediatric heart transplant recipient: Emergence of donor-specific antibodies. *J Heart Lung Transplant.* 2020;39(7):732-733.

112. Xu JJ, Samaha D, Mondhe S, Massicotte-Azarniouch D, Knoll G, Ruzicka M. Renal infarct in a COVID-19-positive kidney-pancreas transplant recipient. *Am J Transplant.* 2020.
99. Jang K, Khatri A, Majure DT. COVID-19 leading to acute encephalopathy in a patient with heart transplant. J Heart Lung Transplant. 2020;39(8):853-855.

100. Westhoff TH, Seibert FS, Bauer F, et al. Allograft infiltration and meningoencephalitis by SARS-CoV-2 in a pancreas-kidney transplant recipient. Am J Transplant. 2020.

101. Del Bello A, Marion O, Sallusto F, et al. Kidney transplantation during the COVID-19 pandemic: Potential long-term consequences of an early post-transplant infection. Transpl Infect Dis. 2020;e13446.

102. Rinaldi M, Bartoletti M, Bussini L, et al. COVID-19 in solid organ transplant recipients: no difference in survival compared to general population. Transpl Infect Dis. 2020;e13421.

103. Latif F, Farr MA, Clerkin KJ, et al. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. JAMA Cardiol. 2020.

104. Verleden GM, Godinas L, Lorent N, et al. COVID-19 in lung transplant patients: A case series. Am J Transplant. 2020.

105. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFEY. Nature. 2020;584(7821):430-436.

106. Goss MB, Galvan NTN, Ruan W, et al. The pediatric solid organ transplant experience with COVID-19: An initial multi-center, multi-organ case series. Pediatr Transplant. 2020;13868.

107. Carfi A, Bernabei R, Landi F. Gemelli against C-ACS-G. per- sequences of an early post- transplant infection. Transpl Infect Dis. 2020;117(20):10970-10975.

108. Bullard J, Dust K, Funk D, et al. Predicting infectious SARS-CoV-2 in two kidney transplant recipients. Transpl Infect Dis. 2020;e13451.

109. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of SARS-CoV-2 in patients with Covid-19 - preliminary report. BMJ. 2020;371:m3939.

110. World Health Organisation. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. Interim guidance. 2020; https://www.who.int/publications/i/item/antig en-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid -immunoassays. Accessed September 27, 2020.

111. Wang AX, Quintero Cardona O, Ho DY, Buesque S, Lenihan CR. Influence of immunosuppression on seroconversion against SARS-CoV-2 in two kidney transplant recipients. Transpl Infect Dis. 2020;e13423.

112. Babel N, Anft M, Blazquez-Navarro A, et al. Immune monitoring facilitates the clinical decision in multifocal COVID-19 of a pancreas-kidney transplant patient. Am J Transplant. 2020.

113. Candon S, Guerrout D, Drouot L, et al. T cell and antibody responses to SARS-CoV-2: Experience from a French transplantation and hemodialysis center during the COVID-19 pandemic. Am J Transplant. 2020.

114. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multi-centre retrospective matched cohort study. Hong Kong Med J. 2003;9(6):399-406.

115. Kim UJ, Won EJ, Kee SJ, Jung SI, Jang HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome. Antivir Ther. 2016;21(5):455-459.

116. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis. 2020;221(11):1762-1769.

117. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949.

118. McCreary EK, Angus DC. Efficacy of remdesivir in COVID-19. JAMA. 2020;324(11):1041-1042.

119. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222.

120. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of COVID-19 – Final Report. N Engl J Med. 2020.

121. Pan H, Peto R, Abdool Karim Q, et al. Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results. medRxiv. 2020.

122. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest. 2020;130(9):4791-4797.

123. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. JAMA. 2020;324(5):460-470.

124. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020;371:m3939.

125. Naeem S, Gohh R, Bayliss G, et al. Successful recovery from COVID-19 in three kidney transplant recipients who received convalescent plasma therapy. Transplant Infect Dis. 2020;e13451.

126. Jiang J, Miao Y, Zhao Y, et al. Convalescent plasma therapy: Helpful treatment of COVID-19 in a kidney transplant recipient presenting with serve clinical manifestation and complex complications. Clin Transplant. 2020;e14025.

127. Noy-Porat T, Makdassi E, Alcalay R, et al. A panel of human neutralizing mAbs targeting SARS-CoV-2 spike at multiple epitopes. Nat Commun. 2020;11(1):4303.

128. Pinto D, Park YJ, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature. 2020;583(7815):290-295.

129. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. 2020.

130. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-10975.

131. Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. Lancet Rheumatol. 2020;2(10):e603-e612.

132. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. JAMA Intern Med. 2020.

133. Group RC, Horby P, Mafham M, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. 2020.

134. Perez-Saez MJ, Blasco M, Redondo-Pachon D, et al. Use of tocilizumab in kidney transplant recipients with COVID-19. Transpl Infect Dis. 2020;in press.

135. Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. Lancet Rheumatol. 2020;2(10):e603-e612.

136. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. JAMA Intern Med. 2020.

137. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020.

138. Perez-Saez MJ, Blasco M, Redondo-Pachon D, et al. Use of tocilizumab in kidney transplant recipients with COVID-19. Am J Transplant. 2020.

139. Pereira MR, Aversa MM, Farr MA, et al. Tocilizumab for severe COVID-19 in solid organ transplant recipients: a matched cohort study. Am J Transplant. 2020.

140. Group RC, Horby P, Lim WS. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med. 2020.
141. Group WHOREAF-C-TW, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA. 2020;324(13):1330-1341.

142. Titanj BK, Farley MM, Mehta A, et al. Use of baricitinib in patients with moderate and severe COVID-19. Clin Infect Dis. 2020.

143. Huet T, Beausser H, Voisin Q, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020;2(7):e393-e400.

144. Diurno F, Numis FG, Porta G, et al. Eculizumab treatment in COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. Eur Rev Med Pharmacol Sci. 2020;24(7):4040-4047.

145. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2018;102(6):900-931.

146. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020;181(5):1036-1045 e1039.

147. Abadja F, Atemkeng S, Alamartine E, Berthoux F, Mariat C. Impact of mycophenolic acid and tacrolimus on Th17-related immune response. Transplantation. 2011;92(4):396-403.

148. Ahmad SH, Smith R, Camilleri B. Belatacept, kidney transplant recipients: A single-center experience with patients immediately after transplantation. Transpl Infect Dis. 2020;20(7):1947-1948.

149. Romanelli A, Mascolo S. Immunosuppression drug-related and infectious complications of COVID-19: a cohort study. Am J Transplant. 2020;181(5):1036-1045 e1039.

150. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;323(18):1843-1844.

151. Romanelli A, Mascolo S. Immunosuppression drug-related and infectious complications of COVID-19: a cohort study. Am J Transplant. 2020;181(5):F1136-F1137.

152. American Society of Transplantation. Information for transplant professionals and community members regarding 2019 novel coronavirus. 2020. https://www.myast.org/information-transplant-professionals-and-community-members-regarding-2019-novel-coronavirus. Accessed September 27, 2020.

153. Rouphael C, D’Amico G, Ricci K, et al. Successful orthotopic liver transplantation in a patient with a positive SARS-CoV2 test and acute liver failure secondary to acetaminophen overdose. Am J Transplant. 2020.

154. Hong HL, Kim SH, Choi DL, Kwon HH. A case of coronavirus disease 2019-infected liver transplant donor. Am J Transplant. 2020;20(10):2938-2941.

155. Han W, Zhu M, Chen J, et al. Lung transplantation for elderly patients with end-stage COVID-19 pneumonia. Ann Surg. 2020;272(1):e33-e34.

156. Chen JY, Qiao K, Liu F, et al. Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. Chin Med J (Engl). 2020;133(12):1390-1396.

157. Bharat A, Querrey M, Markov NS, et al. Lung transplantation for COVID-19-associated acute respiratory distress syndrome in a PCR-positive patient. Lancet Respir Med. 2020;8(10):1057-1060.

158. Lang C, Jaksh P, Hoda MA, et al. Lung transplantation for COVID-19-infected pulmonary fibrosis. Am J Transplant. 2020;20(10):615-632.

159. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol. 2020;20(10):615-632.

160. World Health Organisation. Draft landscape of COVID-19 candidate vaccines. 2020. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

How to cite this article: Danziger-Isakov L, Blumberg EA, Manuel O, Sester M. Impact of COVID-19 in solid organ transplant recipients. Am J Transplant. 2021;21:925–937. https://doi.org/10.1111/ajt.16449