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Transplant/Immunocompromised Hosts (M Morales, Section Editor)

COVID-19 in Solid Organ Transplant Recipients: a Review of the Current Literature

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Abstract

Purpose of review The approach to ongoing organ transplantation and management of COVID-19 in solid organ transplant recipients (SOTR) has evolved tremendously since the pandemic's beginning. We summarize the current literature surrounding the virology of SARS-CoV-2, epidemiology of COVID-19 in transplant recipients, review the clinical features and complications of COVID-19 in SOTR, and discuss the safety and efficacy of current therapies and candidate vaccines in this population.
Recent findings Despite initial suspensions in organ transplantation during early 2020, routine donor testing and de-crowding of hospitals have allowed transplant activity to resume at pre-pandemic rates. COVID-19-associated mortality in SOTR is similar to that of the general population, and lower than that of patients with end-organ disease awaiting transplant. The optimal approach to immunosuppression in SOTR with COVID-19 is unknown and disease severity may influence management decisions. Many vaccines in development are likely to be safe for immunocompromised hosts, though post-marketing investigations will be required to determine the efficacy in the SOTR.
Summary Though there are multiple unique considerations in the care of SOTR with COVID-19, immunosuppression does not appear to have a detrimental impact on overall outcome. Organ transplantation remains a lifesaving intervention and can be safely performed despite a global pandemic.

Introduction

The impact of the COVID-19 pandemic on the field of solid organ transplantation has been profound, from patients with organ transplants to patients on waiting lists to clinicians and transplant programs. Over the first year since the emergence of the novel coronavirus, SARS-CoV-2, in 2019, several key questions about COVID-19 in transplantation have arisen: How is the epidemiology of COVID-19 different for transplant recipients? What are the clinical manifestations and outcomes of COVID-19 in patients with organ transplants? What role does immunosuppression play in infection, morbidity, and mortality? What are the optimal strategies for treatment or prevention of COVID-19 among transplant recipients? How should transplant programs adapt to the novel global pandemic in order to deliver optimal care to their patients? This review will summarize current knowledge about COVID-19 in transplantation.

Virology and immunology

SARS-CoV-2 is a novel human beta-coronavirus of probable bat origin first recognized in Wuhan, China, in late 2019 [1]. All coronaviruses are large, enveloped, positive-sense RNA viruses with 4 homologous structural proteins: envelope, membrane, nucleocapsid, and spike. The spike protein of SARS-CoV-2 binds angiotensin-converting enzyme 2 (ACE2) on the human cell surface. The SARS-CoV-2 spike protein receptor-binding domain is hidden in the pre-activation state, enabling immune evasion. Multiple host proteins including furin, TMPRSS2, and lysosomal proteases participate in SARS-CoV-2 entry into human cells by exposing the receptor-binding domain and facilitating endocytosis, leading to high-affinity binding to ACE2 and enhanced cell entry [2]. These unique properties of the cell entry molecular mechanism may contribute to infectivity and impaired immune clearance of the virus.

ACE2 is widely distributed in human tissue including in the lung, heart, kidney, central nervous system, and vascular endothelium [3]. SARS-CoV-2 has been detected in each of these tissues in clinical samples or at autopsy in a limited number of cases, although detection of intact virions by electron microscopy remains a technical challenge requiring specialized expertise [4–6]. Direct viral infection of non-lung tissues may contribute to organ-specific involvement and extra-pulmonary symptoms seen in COVID-19, including renal dysfunction, cardiomyopathy, vasculopathy, and more recently recognized neuropsychiatric effects [7]. The possibility of non-lung end organ involvement with SARS-CoV-2 has raised the question of whether SARS-CoV-2 could be transmitted through transplantation. In the USA, the Organ Procurement and Transplantation Network (OPTN) recommends that all potential deceased organ donors be screened for SARS-CoV-2 infection and that any potential donor who tests positive be deferred [8]. One case report describes inadvertent living liver transplantation from a donor with symptomatic SARS-CoV-2 infection at the time of donation, without transmission [9].

Early infection appears to be dominated by viral replication. In later infection, host immune dysregulation appears to play a significant role in the pathogenesis of severe COVID-19 and respiratory failure, as well as delayed sequelae of COVID-19 [10]. Plasma cytokine levels indicate broad immune activation including type 1, 2, and 3 responses, with some evidence that a type 2

immune response may be more strongly associated with respiratory failure [11]. How transplant-related maintenance immunosuppression affects this complex pathophysiology is still incompletely understood and likely varies with the different phases of illness. Interestingly, while short-term application of glucocorticoids is shown to reduce the type 2 immune response, prior exposure to glucocorticoids is associated with a predisposition toward type 2 immunity, which may partially explain the therapeutic value of glucocorticoids despite some evidence in non-transplant populations that baseline steroid use is not protective [12–14].

Epidemiology

As of March 30, 2021, there have been over 127 million cases of COVID-19 diagnosed, and over 2.7 million deaths globally [15]. Seroprevalence studies suggest that confirmed case counts underestimate the true prevalence of COVID-19 by a factor of 10 [11]. Following its emergence in Wuhan, China, the early phases of the COVID-19 pandemic were defined by travel-associated local and regional outbreaks, with notable large outbreaks in Italy, Iran, Spain, and New York City, USA, from February through April 2020 [16] (Table 1). During this period, concerns about unfavorable outcomes among organ transplant recipients, challenges with infection prevention and control, and reduced resource availability led to a decline in deceased donor organ transplantation by 51% in the USA and as high as 91% in France [17]. Such declines in transplantation were associated with increases in waitlist deaths [18, 19]. Despite the continued rise in cases, transplantation has returned to pre-2020 levels in many regions, reflecting the adaptability of the transplant community and increasing understanding of the risks of deferring transplantation for patients on waiting lists.

SARS-CoV-2 is spread primarily via respiratory droplets, with additional contributions from short-distance aerosols and contaminated surfaces [11]. Multiple epidemiologic studies have demonstrated higher incidence of COVID-19 among solid organ transplant recipients compared to the general population, which may be due to increased risk of exposure from frequent healthcare contacts, greater susceptibility to a lower infectious dose of SARS-CoV-2, greater likelihood of symptomatic rather than asymptomatic infection, or ascertainment bias due to increased alertness and testing in this population [20, 21]. Interestingly, studies in Italy and the UK reveal even higher incidence among patients on transplant waiting lists, again underscoring the risks of deferring transplantation during this pandemic [22, 23].

Transplant recipients may also be more likely to transmit SARS-CoV-2. In the general population, peak viral shedding occurs prior to symptom onset and declines rapidly [11]. Among immunocompromised transplant patients, viral shedding may persist much longer and at lower cycle thresholds, corresponding to higher viral loads [24]. Although detection of viral RNA does not necessarily indicate transmissible live virus, altered viral kinetics in transplant recipients may have implications for infection prevention. Neutralizing antibodies to SARS-CoV-2 typically appear at approximately 2 weeks after symptom onset. The degree of protection and duration of natural immunity is not yet fully understood and may differ for transplant recipients. In one study of kidney

Table 1. Largest cohort studies of solid organ transplant recipients with COVID-19

Study	Setting	Recruitment period	Subjects	Mortality
Kates et al [4]	Majority USA	March 1 - April 15	482 318 Kidney 73 Liver 57 Heart 30 Lung 4 Other	20.5% (hospitalized) 18.7% (overall)
Colmenero & Rodríguez- Perálvarez et al [21]	Spain	February 28 - April 7	111 Liver	20.8% (hospitalized) 18% (overall)
Ravanan & Callaghan et al [23]	UK	February 1 - May 20	597 470 Kidney 19 SPK 3 Pancreas 64 Liver 23 Heart 13 Lung 2 Intestine 3 Multiple	25.8% (overall)
Favà & Cucchiari et al [29]	Spain	March 4 - April 17	104 Kidney	26.9% (hospitalized)
Cravedi & Mothi et al [30]	International (USA, Italy, Spain)	March 2 - May 15	144 Kidney	31.9% (hospitalized)
Webb & Marjot et al [32]	International	March 25 - June 26	151 Liver	22% (hospitalized) 19% (overall)
Coll et al [33]	Spain	February 20 - July 13	665 423 Kidney 110 Liver 69 Heart 54 Lung 8 Pancreas 1 Multiple	24.7% (overall)
Mansoor et al. [78]	USA	January 1 - June 23	126 Liver	20% (hospitalized) 7.9% (overall)

Study	Additional outcomes	Risk factors for mortality	Comparison to non-SOTR
Kates et al [4]	78% required hospitalization *Among hospitalized patients* 39.1% required ICU	Age >65 Congestive heart failure Chronic lung disease Obesity Lymphopenia	*Compared to pooled weighted average mortality for multiple general population cohorts* SOTR had similar mortality (20.5% vs. 19.3%)

Table 1. (Continued)

Study	Additional outcomes	Risk factors for mortality	Comparison to non-SOTR
	31.1% required mechanical ventilation 44.4% AKI 14.6% RRT 1.1% Allograft rejection 8.8% secondary respiratory infection	Radiographic evidence of pneumonia	
Colmenero & Rodríguez-Perálvarez et al [21]	86.5% required hospitalization *Among hospitalized patients* 12.5% required ICU 9.4% required mechanical ventilation	***Risk factors for composite endpoint of ICU, respiratory support, or death*** Male gender Charlson comorbidity index Dyspnea Mycophenolate-containing maintenance immunosuppression	*Compared to an age- and gender-matched general population cohort* No difference in mortality
Ravanan & Callaghan et al [23]		Age	*Compared to U.K. patients on a transplant waiting list* SOTR had lower rate of infection (1.3% vs. 3.8%) SOTR had higher mortality (25.8% vs. 10.2%) *Compared to a general population study (Docherty et al.)*[4] No difference in mortality
Favà & Cucchiari et al [29]	*Among hospitalized patients* 13.6% required mechanical ventilation 47% AKI 0% Allograft rejection	***Univariable analysis only*** Age Pulmonary disease Active malignancy Nosocomial infection Hypoxemia Cadaveric donor organ Extended criteria donor organ	None
Cravedi & Mothi et al [30]	*Among hospitalized patients* 30% Required ICU 29% Mechanical ventilation 51% AKI	***Univariable analysis only*** Age >60 Dyspnea Tachypnea Absence of diarrhea Lymphopenia Reduced EGFR Elevated AST Elevated LDH	None

Table 1. (Continued)

Study	Additional outcomes	Risk factors for mortality	Comparison to non-SOTR
		Elevated IL-6 Elevated procalcitonin	
Webb & Marjot et al [32]	82% Required hospitalization *Among hospitalized patients* 35% Required ICU 24% Required mechanical ventilation	Age Non-liver malignancy Elevated creatinine	*In a propensity score-matched analysis with 627 non-SOTR* No difference in mortality *Without matching* SOTR had a higher rate of ICU admission and mechanical ventilation
Coll et al [33]	76.4% Required hospitalization *Among hospitalized patients* 14.8% Required ICU 9.8% Required mechanical ventilation	***Univariable analysis only*** Age Lung transplant Nosocomial infection	None
Mansoor et al. [78]	40% Required hospitalization *Among hospitalized patients* 20% Required ICU		*In a propensity score-matched analysis with 125 non-SOTR* No difference in mortality SOTR had a higher risk of hospitalization

transplant recipients, antibodies to SARS-CoV-2 emerged within the second week after symptoms and persisted for 2 months for all patients [25]. Case reports describe non-immunosuppressed patients who have developed SARS-CoV-2 re-infection after seroconversion [26]. Although there are no case reports of re-infection in solid organ transplant recipients, one report does describe a patient who developed COVID-19 prior to liver transplantation and proceeded to seroconversion and negative SARS-CoV-2 nasopharyngeal swab PCRs. The patient received a deceased donor liver transplant from a donor who tested negative for SARS-CoV-2 on day 36 after symptom onset, day 15 after seroconversion. After transplant, the patient had return of positive nasopharyngeal swab PCR for SARS-CoV-2 that was genetically identical to the previous strain, as well as marked decline in neutralizing antibodies to a low-range titer [27]. This single case suggests that the process of transplantation, whether the stress of surgery, hemodilution, or immunosuppression, could potentially affect SARS-CoV-2 natural immunity that could theoretically predispose some transplant patients to reinfection, although actual cases of reinfection are not yet reported.

Clinical course and outcomes

Among solid organ transplant recipients with COVID-19, approximately half have fever at presentation, a majority have cough and dyspnea, one-third have upper respiratory symptoms, and between one-third and one-half have gastrointestinal symptoms [17, 20, 28, 29]. In one study, 5% of patients presented with gastrointestinal symptoms in the absence of any respiratory symptoms [17]. Even in patients with minimal or mild respiratory symptoms, radiographic evidence of pneumonia is very common, seen in over 80% of patients [17, 30]. Differing definitions of clinical criteria, particularly "fever," have led to a wide range in reported rates of some symptoms; however, when comparable definitions are considered, the symptom profile among solid organ transplant recipients with COVID-19 is essentially the same as for the general population [17].

During the early phases of the COVID-19 pandemic, solid organ transplant patients experienced high morbidity and mortality. In the USA, approximately 75% of solid organ transplant recipients diagnosed with COVID-19 required hospital admission. Of these, close to 40% required intensive care, close to 30% required mechanical ventilation, and 25% required vasopressor support [17, 28]. Mortality among hospitalized patients in large cohorts of solid organ transplant recipients with COVID-19 has ranged from 20 to 32% [17, 21, 23, 28–33]. Although these outcomes are grave, mortality appears to be similar to hospitalized general population cohorts during the same time period [34]. In fact, one study found significantly lower mortality among liver transplant recipients than in a matched comparison cohort [21]. More recently, morbidity and mortality from COVID-19 appear to be declining in the general population, possibly due to increased testing and identification of mild cases, changing epidemiology with a higher proportion of young patients with fewer comorbidities, improvements in management, or resource availability [11].

Risk factors for mortality among solid organ transplant recipients with COVID-19 include older age, underlying medical conditions such as obesity, chronic lung disease, congestive heart failure, or malignancy and features of

severe COVID-19 at presentation such as leukopenia or radiographic evidence of pneumonia [17, 32]. In one large cohort study including 54 lung transplant recipients, lung transplantation was associated with an increased risk of mortality compared to non-lung transplant recipients in a univariable analysis; however, this study was not able to control for baseline comorbidities [33]. In another study including 30 lung transplant recipients, there was a trend toward increased mortality among lung transplant recipients in a univariable analysis, but no association between type of organ transplanted and mortality in a model adjusted for age and comorbidities [17]. To date, no study has demonstrated a significant independent relationship between the timing of transplant or recent induction immunosuppression with mortality from COVID-19. In addition, no specific maintenance immunosuppression regimen or drug has been shown to be associated with mortality among transplant recipients with COVID-19. However, in one study of liver transplant recipients, use of a mycophenolate-containing maintenance immunosuppression regimen was associated with a composite endpoint of ICU admission, mechanical ventilation, or death [21]. In general, the preponderance of evidence supports that age and comorbidities, rather than immunosuppression-related factors, drive COVID-19 mortality among solid organ transplant recipients. Similar findings are reported for patients with inflammatory bowel disease and patients with malignancy [35–37].

Acute kidney injury

The reported incidence of acute kidney injury (AKI) in hospitalized patients with COVID-19 ranges from 0.5 to 50%, with lower incidences reported in China compared to Europe and the USA [38–40]. High FiO2 requirements, mechanical ventilation, vasopressor use, advanced age, male sex, Black race and underlying hypertension, diabetes mellitus, or chronic kidney disease are risk factors for AKI in the setting of COVID-19 [38, 39, 41, 42].

Solid organ transplant recipients with COVID-19 are at particularly high risk for kidney injury due to high prevalence of underlying chronic kidney disease, diabetes mellitus, hypertension, and calcineurin inhibitor (CNI) use. In a multicenter study of 482 SOTR with COVID-19, 44% of hospitalized patients developed AKI and 15% required renal replacement therapy [17]. Smaller studies directly comparing SOT recipients versus non-SOT controls show trends towards higher incidences of AKI requiring RRT in SOT recipients, even when controlling for underlying CKD [31, 43]. Diarrhea, present in nearly half of SOTR with COVID-19 [17], reduces efflux pump expression from intestinal epithelial cells, leading to toxic CNI troughs [44]. Treatment of COVID-19 using ritonavir or cobicistat-boosted protease inhibitors may lead to substantial increases in CNI levels and resulting nephrotoxicity by impairing cytochrome P450 drug metabolism [45].

Allograft rejection and dysfunction

Allograft dysfunction in COVID-19 must be differentiated from allograft rejection, as heart, lung, kidney, and liver injuries are well-described sequelae of SARS-CoV-2 infection in the non-SOT population. Cytomegalovirus (CMV)

and other viral infections enhance alloantigen reactivity, raising the question as to whether SOTR with COVID-19 are at risk for allograft rejection [46]. Any reduction immunosuppression in response to diagnosis of a viral illness would further the risk of rejection. Literature regarding allograft rejection in COVID-19 is currently limited, though biopsy-proven kidney and liver rejection has been reported [47–50]. In a series of 482 SOTR with COVID-19 followed for 28 days, acute cellular rejection (ACR) occurred in 6 patients (1.3%) and antibody-mediated rejection occurred in one patient [17]. Thus, allograft rejection in COVID-19 appears to be rare, though ascertaining the true incidence of biopsy-proven rejection in patients with COVID-19 may be limited by reluctance to perform invasive procedures for infection control purposes.

Concurrent infections

Patients with COVID-19 may have viral, bacterial, or fungal infections at any time during their course of illness. Injury to the respiratory tract epithelium and loss of ciliary function predisposes individuals with influenza and other respiratory viruses to secondary pulmonary infections. In large, single-center studies of the general population, secondary infections occurred in 3–5% of hospitalized patients with COVID-19 [51, 52], though smaller studies and meta-analyses suggest that the true incidence in patients surviving the initial phase of illness may be higher [53]. The largest cohort study of hospitalized SOTR with COVID-19 to date demonstrates a similar, but slightly higher, incidence of secondary infection; 8% and 6.1% developed bacterial pneumonia and bloodstream infections during hospitalization, respectively [17]. Bacterial pathogens were most common; two patients were diagnosed with Aspergillus pneumonia, and one patient each was diagnosed with Cryptococcus and Pneumocystis pneumonia [17]. Pulmonary aspergillosis in both immunocompetent and immunocompromised patients with COVID-19 has been reported and is associated with poor outcomes [54].

Treatment of COVID-19

Effective pharmacotherapy for COVID-19 remains limited and data on treatment efficacy is SOTR is sparse. Current treatment strategies focus on [1] inhibiting viral entry and replication and [2] mitigating an overactive immune response to the virus. Remdesivir, a broad-spectrum antiviral which inhibits viral RNA-dependent RNA polymerase, has received emergency use authorization from the Food and Drug administration (FDA). This approval was based on data from the Adaptive COVID-19 Treatment Trial-1 (ACTT-1), a large randomized, placebo-controlled trial demonstrating a trend toward improved survival in severely ill patients and improved respiratory status in hypoxemic patients not requiring intubation [17, 55]. However, preliminary results of the SOLIDARITY trial, a multinational randomized control trial, do not suggest that remdesivir has any impact on mortality. Seven percent of patients in the ACTT-1 trial were classified as having an immune deficiency, but details of these immune compromising states were not reported [55]. Early anti-viral therapy lessens influenza disease severity in solid organ transplant recipients [56]; the impact of timely remdesivir administration in SOTR with COVID-19 has not been delineated.

Convalescent plasma from donors who have recovered from SARS-CoV-2 infection provides passive immunity with the goal of preventing viral entry and nucleic acid assembly. The US Food and Drug Administration (FDA) has issued an emergency use authorization for use for convalescent plasma, but data supporting its efficacy are limited to small reports [57, 58]. For solid organ transplant recipients, convalescent plasma offers the advantage of avoiding the potential for nephrotoxicity and drug-drug interactions, and immunosuppression does not preclude participation in clinical trials. Several anti-spike protein monoclonal antibodies have been authorized for emergency use. Administration of a monoclonal antibody shortly after exposure provides passive immunity and may dampen disease severity [59].

Several other drugs with antiviral activity have been explored. Despite initial enthusiasm for chloroquine and hydroxychloroquine, these agents have not been proven to be effective in treating COVID-19 [60, 61], leading to revocation of an FDA-issued emergency use authorizations [61]. Several other agents, including azithromycin, ivermectin, HIV protease inhibitors, and ribavirin, demonstrate in vitro activity against SARS-CoV-2 or other coronaviruses, but grounded evidence supporting their clinical use in either the general or immunocompromised population is lacking [57].

Anti-inflammatory agents used to inhibit an overactive immune response have shown mixed results. The corticosteroid dexamethasone was shown to decrease mortality in patients with severe COVID-19 requiring supplemental oxygen in a large, randomized, open labeled control trial (RECOVERY) [62], though methylprednisolone did not demonstrate such benefit in a phase IIb double-blinded study [63]. Monoclonal antibodies directed against interleukin 6 (IL-6), the IL-6 receptor, and interleukin-1β are under investigation but are not recommended for use outside of clinical trials [64, 65]. Janus kinase (JAK) inhibitors including baracitinib and ruxolitinib are currently under investigation for use in COVID-19, as these agents have in vitro antiviral properties and interfere with cytokine signaling [66]. Whether the addition of dexamethasone or other anti-inflammatory therapies benefits solid-organ transplant patients who are immunosuppressed at presentation is unclear, as immunosuppression precluded enrollment in many large-scale, randomized studies. Concerns that dexamethasone, in combination with other immunosuppressants, may increase the risk of co-infections and prolong shedding of live virus further complicate management decisions in SOTR with COVID-19 (Table 2).

Management of immunosuppression

The optimal management of immunosuppression in patients with COVID-19 is unknown. Decreasing or withdrawing immunosuppression to promote viral clearance is an intuitive management strategy employed for treatment of severe viral infections in SOTR. However, the hyper-inflammatory response characteristic of severe COVID-19 has introduced a hypothesis that immunosuppression may be protective against severe disease and the observed benefits of dexamethasone support a role for immune modulation in disease management [62]. Indeed, solid organ transplant recipients with sepsis and bacteremia have improved outcomes compared to controls, suggesting that immunosuppression may curb the detrimental effects of hypercytokinemia [68]. However, there

is little evidence that the immunosuppression used in the post-transplant setting impacts cytokine profiles in COVID-19. IL-6 and CRP levels, both evidence of cytokine release and predictors of poor outcomes in COVID-19 [69], were similar among SOTR and non-SOTR in a multicenter analysis [31]. In vitro suggestions that mycophenolate and tacrolimus have direct activity against coronaviruses provided an initial argument in favor of continuing full-dose immunosuppression, but in vivo evidence of benefit is lacking [70].

Unlike other respiratory viruses, SARS-CoV-2 viral burden peaks early after infection prior to development of prominent symptoms [71], and severe illness develops late in the course when viral replication has diminished. Thus, reducing immunosuppression in early COVID-19 to promote viral clearance may prevent progression to severe disease is an intuitive approach. Because lymphopenia portends a poor prognosis in COVID-19 [69], limiting exposure to lymphotoxic immunosuppressive agents (e.g., mycophenolate) is logical. Reducing immunosuppression (RIS), particularly antimetabolites, has demonstrable impacts on controlling DNA viruses in SOTR [72]. Evidence supporting RIS for lower respiratory viral infections is less robust, though, as discussed above, withdrawal of maintenance mycophenolate was associated with a trend toward less severe COVID-19 disease in a cohort of liver transplant recipients in Spain [21]. Holding or reducing antimetabolites has become a common practice in the management of SOTR with COVID-19, while adjustments to calcineurin inhibitors are less common [17, 28, 43, 46]. Addition of dexamethasone in severe disease provides additional protection against allograft rejection.

Vaccines

Vaccines are powerful tools for controlling pandemic respiratory viruses [73]. In December 2020, two vaccines containing messenger RNA encoding the SARS-CoV-2 spike protein (mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech)) were authorized for emergency use in many countries based on promising efficacy data from phase III trials in immunocompetent adults [74, 75]. Replication-defective adenoviral vaccines containing the DNA version of the SARS-CoV-2 spike protein and vaccines that contain whole-inactivated SARS-CoV-2 virus or recombinant spike proteins are platforms that have also been authorized for use or in advanced phases of clinical trials [76]. These major vaccine platforms do not contain any replication-competent SARS-CoV-2 RNA and therefore do not pose any risk of SARS-CoV-2 infection in immunocompromised hosts. There is a theoretical risk that any vaccine may elicit systemic immune response and subsequent rejection. This became a major concern after a high incidence of de novo anti-HLA antibodies was observed in kidney transplant recipients who received the 2009 influenza A(H1Na1)pdm09 vaccine. However, a thorough investigation was unable to identify any association between vaccination and acute rejection and multiple professional organizations agree that the potential benefits of SARS-CoV-2 vaccination far exceed any theoretical risks [76].

While the SARS-CoV-2 platforms in current use do not have major safety concerns for SOT recipients, it is unknown whether these vaccines will be sufficiently immunogenic and effective in immunocompromised populations. Solid organ transplant recipients on immunosuppressive agents are precluded from participating in SARS-CoV-2 vaccine trials. SOTR mount weaker antibody

Table 2. Prophylactic and therapeutic agents for COVID-19: considerations for solid organ transplant recipients

	Comments regarding use in general population	Comments regarding use in SOTR
Direct antivirals		
Remdesivir (RNA polymerase inhibitor)	Improvement in respiratory status in hypoxemic patients not requiring intubation; no significant reduction in mortality demonstrated [55].	SOTR eligible for enrollment in RCTs, no subgroup analysis available.
Favipiravir (RNA polymerase inhibitor)	Limited RCT data, reduced viral clearance time and CT scans compared to LPV/r in an 80-person open label trial [67]; approved for use in Russia [66].	Case reports in SOTR with COVID-19.[4, 5]
Lopinavir/ritonavir (protease inhibitor)	No benefit in time to clinical improvement in hospitalized adults (81).	CYP inhibition, CNI toxicity reported[7]
Other (hydroxychloroquine +/- azithromycin, famotidine, ivermectin)	Not recommended for routine use; risk may outweigh benefit [65].	SOTR eligible for RCTs but number enrolled not consistently reported.
Viral entry inhibitors		
Convalescent plasma	Approved under EUA [65].	Theoretical risk of increased panel antibody reactivity.
Monoclonal antibodies	Approved under EUA [59].	SOTR eligible for RCTs.
Anti-inflammatory agents		
IL-6/IL-6R monoclonal antibodies (tocilizumab, sarilumab, siltuximab)	No evidence of benefit or harm in COVID-19 related mortality; possible increase in secondary infections [65].	SOTR excluded from RCTs.
JAK inhibitors (ruxolitinib, baracitinib)	Direct antiviral activity and inhibition of cytokine signaling.	SOTR excluded from RCTs.
Corticosteroids	Decrease mortality in severe disease [65].	SOTR excluded from RCTs.
Active immunization (vaccines)		
Nucleic acid	No non-SARS-CoV-2 nucleic vaccine in clinical use; 2 mRNA vaccines available under EUA.	Safe in theory, One study shows similar adverse events to general population but low antibody response in SOTR after first dose. [67]
Viral vector	Multiple adenovirus and vesicular stomatitis vector vaccines in Phase III clinical trials. 1 adenovirus vector vaccine available under EUA.	Replication deficient vectors likely safe in SOTR; unknown safety of replicating vectors; SOTR excluded from RCTs
Recombinant protein	Nanoparticle and adjuvant-boosted	Immunogenic adjuvants pose theoretical risk of rejection; SOTR excluded from RCTs
Whole, inactivated virus	Approved for limited use in China	Safe in theory, SOTR excluded from RCTs
Live, attenuated virus	Pre-clinical investigations	Not safe for use in immunocompromised hosts

responses to inactivated, polysaccharide, and conjugated vaccines compared to healthy controls and preliminary data suggests that SOT recipients may mount weaker humoral responses to mRNA SARS-CoV-2 vaccines compared to healthy controls [67, 77]. Large epidemiologic studies assessing the real-world effectiveness of vaccines in preventing both severe infection and asymptomatic transmission in SOT recipients are desperately needed.

Conclusions and future directions

Our understanding of the SARS-CoV-2 virology and COVID-19 disease has grown tremendously over the past 9 months. Outcomes of COVID-19 in SOTR appear to mirror those in the general population, though how to best balance the protective and deleterious aspects of immunosuppression remains uncertain. Dedicated efforts are needed to understand the efficacy of novel treatments and vaccines in solid organ transplant recipients and immunocompromised hosts. Despite continued uncertainty about the management of COVID-19 after transplantation, the risks of deferring transplantation for patients on waiting lists must be appreciated, and we commend transplant programs around the world for their work to continue to deliver this life-saving therapy under extraordinarily challenging circumstances.

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Compliance with ethical standards

Conflict of interest
M.R.H reports receiving speaking fees from Cigna LifeSource. O.S.K has no relevant interests to disclose.

Human and animal rights and informed consent
The article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer
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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Narh CA. Genomic cues from beta-coronaviruses and mammalian hosts sheds light on probable origins and infectivity of SARS-CoV-2 causing COVID-19. Front Genet. 2020;11:902.
2. Shang J, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020;117:11727–34.
3. Hammoud S, et al. Dysregulation of ACE2 expression and function in co-morbid disease conditions possibly contributes to COVID-19 complication severity. Mol Pharmacol. 2020.
4. Kates OS, Fisher CE, Rakita RM, Reyes JD, Limaye AP. Use of SARS-CoV-2-infected deceased organ donors: Should we always "just say no?". Am J Transplant. 2020;20:1787–94.
5. Puelles VG, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med. 2020;383:590–2.
6. Dittmayer C, et al. Why misinterpretation of electron micrographs in SARS-CoV-2-infected tissue goes viral. Lancet. 2020;396:e64–5.
7. D'Errico S, et al. More than pneumonia: distinctive features of SARS-Cov-2 infection. From autopsy findings to clinical implications: a systematic review. Microorganisms. 2020;8.
8. Organ Procurement and Transplantation Network. U.S. Department of Health and Human Services, 2020.
9. Hong HL, Kim SH, Choi DL, Kwon HH. A case of coronavirus disease 2019-infected liver transplant donor. Am J Transplant. 2020;20:2938–41.
10. Kadkhoda K. COVID-19: an Immunopathological View. mSphere. 2020;5.
11. Fang FC, et al. COVID-19 - lessons learned and questions remaining. Clin Infect Dis. 2020.
12. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. 2015;135:626–35.
13. Strehl C, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-all-rounders tackling the versatile players of the immune system. Front Immunol. 2019;10:1744.
14. Brenner EJ, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. Gastroenterology. 2020;159:481–491.e483.
15. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. 2020. https://covid19.who.int/. Accessed 30 Oct 2020.
16. Dawood FS, et al. Observations of the global epidemiology of COVID-19 from the prepandemic period using web-based surveillance: a cross-sectional analysis. Lancet Infect Dis. 2020;20:1255–62.
17. Kates OS, et al. COVID-19 in solid organ transplant: a multi-center cohort study. Clin Infect Dis. 2020.
18. Strauss AT, et al. Liver transplantation in the United States during the COVID-19 pandemic: national and center-level responses. Am J Transplant. 2020.
19. Domínguez-Gil B, et al. COVID-19 in Spain: Transplantation in the midst of the pandemic. Am J Transplant. 2020;20:2593–8.
20. Tschopp J, et al. First experience of SARS-CoV-2 infections in solid organ transplant recipients in the Swiss Transplant Cohort Study. Am J Transplant. 2020;20:2876–82.
21. Colmenero J, et al. Epidemiological pattern, incidence and outcomes of COVID-19 in liver transplant patients. J Hepatol. 2020.
22. Angelico R, et al. The COVID-19 outbreak in Italy: initial implications for organ transplantation programs. Am J Transplant. 2020;20:1780–4.
23. Ravanan R, 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.
24. Gaston DC, et al. Clinical implications of SARS-CoV-2 cycle threshold values in solid organ transplant recipients. Am J Transplant. 2020.
25. Benotmane I, et al. In-depth virological assessment of kidney transplant recipients with COVID-19. Am J Transplant. 2020.
26. AlFehaidi A, Ahmed SA, Hamed E. A case of SARS-CoV-2 re-infection. J Inf Secur. 2020.
27. Niess H, et al. Liver transplantation in a patient after COVID-19 - rapid loss of antibodies and prolonged Viral RNA Shedding. Am J Transplant. 2020.
28. Pereira MR, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant. 2020;20:1800–8.
29. Favà A, et al. Clinical characteristics and risk factors for severe COVID-19 in hospitalized kidney transplant recipients: a multicentric cohort study. Am J Transplant. 2020.
30. Cravedi P, et al. COVID-19 and kidney transplantation: results from the TANGO International Transplant Consortium. Am J Transplant. 2020.
31. Molnar MZ, et al. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. Am J Transplant.
32. Webb GJ, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international

registry study. Lancet Gastroenterol Hepatol. 2020;5:1008–16.
33. Coll E, et al. Covid-19 in transplant recipients: the spanish experience. Am J Transplant. 2020.
34. Docherty AB, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. Bmj. 2020;369:m1985.
35. Pinato DJ, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. Cancer Discov. 2020.
36. Burke KE, et al. Immunosuppressive therapy and risk of COVID-19 infection in patients with inflammatory bowel diseases. Inflamm Bowel Dis. 2020.
37. Derikx L, et al. Clinical outcomes of Covid-19 in patients with inflammatory bowel disease: a nationwide cohort study. J Crohns Colitis. 2020.
38. Fu EL, et al. Acute kidney injury and kidney replacement therapy in COVID-19: a systematic review and meta-analysis. Clin Kidney J. 2020;13:550–63.
39. Hirsch JS, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98:209–18.
40. Cheng Y, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97:829–38.
41. Fisher M, et al. AKI in hospitalized patients with and without COVID-19: A Comparison Study. J Am Soc Nephrol. 2020;31:2145–57.
42. Pelayo J, et al. Clinical characteristics and outcomes of community- and hospital-acquired acute kidney injury with COVID-19 in a US Inner City Hospital System. Cardiorenal Med. 2020;10:223–31.
43. Sharma P, et al. COVID-19 outcomes among solid organ transplant recipients: a case-control study. Transplantation. 2020.
44. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009;4:481–508.
45. Xia T, Wang Y. Coronavirus disease 2019 and transplantation: the combination of lopinavir/ritonavir and hydroxychloroquine is responsible for excessive tacrolimus trough level and unfavorable outcome. Am J Transplant. 2020;20:2630–1.
46. Roberts MB, et al. COVID-19 in solid organ transplant recipients: dynamics of disease progression and inflammatory markers in ICU and non-ICU admitted patients. Transpl Infect Dis. 2020;2020:e13407.
47. Lagana SM, et al. COVID-19 associated hepatitis complicating recent living donor liver transplantation. Arch Pathol Lab Med. 2020.
48. Heinz N, et al. A case of an infant with SARS-CoV-2 hepatitis early after liver transplantation. Pediatr Transplant. 2020;2020:e13778.
49. Kudose S, et al. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol. 2020;31:1959–68.
50. Zhong Z, et al. Clinical characteristics and immunosuppressant management of coronavirus disease 2019 in solid organ transplant recipients. Am J Transplant. 2020;20:1916–21.
51. Nori P, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. In: Infect Control Hosp Epidemiol; 2020. p. 1–5.
52. Garcia-Vidal C, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2020.
53. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med. 2020.
54. Bartoletti M, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clin Infect Dis. 2020.
55. Beigel JH, et al. Remdesivir for the treatment of Covid-19 - preliminary report. N Engl J Med. 2020.
56. Kumar D, et al. A 5-year prospective multicenter evaluation of influenza infection in transplant recipients. Clin Infect Dis. 2018;67:1322–9.
57. Ali MJ, et al. Treatment options for COVID-19: a review. Front Med (Lausanne). 2020;7(480).
58. Li L, 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;324:460–70.
59. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA. 2020;324:131–2.
60. Cavalcanti AB, et al. Hydroxychloroquine with or without Azithromycin in mild-to-moderate Covid-19. N Engl J Med. 2020.
61. Thomson K, Nachlis H. Emergency use authorizations during the COVID-19 pandemic: lessons from hydroxychloroquine for vaccine authorization and approval. JAMA. 2020.
62. Horby P, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.
63. Jeronimo CMP, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis. 2020.
64. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 19 Sept 2020.
65. Bhimraj A, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis. 2020.
66. Saber-Ayad M, Saleh MA, Abu-Gharbieh E. The rationale for potential pharmacotherapy of COVID-19. Pharmaceuticals (Basel). 2020;13.
67. Boyarsky BJ, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. JAMA. 2021.
68. Kalil AC, et al. Is bacteremic sepsis associated with higher mortality in transplant recipients than in

nontransplant patients? A matched case-control propensity-adjusted study. Clin Infect Dis. 2015;60:216–22.
69. Chen X, Yan L, Fei Y, Zhang C. Laboratory abnormalities and risk factors associated with in-hospital death in patients with severe COVID-19. J Clin Lab Anal. 2020;2020:e23467.
70. Russell B, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience. 2020;14:1022.
71. He X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26:672–5.
72. Weikert BC, Blumberg EA. Viral infection after renal transplantation: surveillance and management. Clin J Am Soc Nephrol. 2008;3(Suppl 2):S76–86.
73. Pagliusi S, Dennehy M, Kim H, Committee DAO. Vaccines, inspiring innovation in health. Vaccine. 2018;36:7430–7.
74. Polack FP, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020.
75. Baden LR, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020.
76. Heldman MR, Limaye AP. SARS-CoV-2 vaccines in kidney transplant recipients: will they be safe and effective and how will we know? J Am Soc Nephrol. 2021.
77. Danziger-Isakov L, Kumar D, A. I. C. o. Practice, Vaccination of solid organ transplant candidates and recipients: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transpl. 2019;33:e13563.
78. Mansoor E, et al. Clinical characteristics, hospitalization and mortality rates of COVID-19 among liver transplant patients in the United States: a multi-center research network study. Gastroenterology. 2020.

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