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The Global Impact of COVID-19 on Solid Organ Transplantation: Two Years Into a Pandemic

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Abstract. The coronavirus disease 2019 (COVID-19) pandemic has had a major global impact on solid organ transplantation (SOT). An estimated 16% global reduction in transplant activity occurred over the course of 2020, most markedly impacting kidney transplant and living donor programs, resulting in substantial knock-on effects for waitlisted patients. The increased severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection risk and excess deaths in transplant candidates has resulted in substantial effort to prioritize the safe restart and continuation of transplant programs over the second year of the pandemic, with transplant rates returning towards prepandemic levels. Over the past 2 y, COVID-19 mortality in SOT recipients has fallen from 20%–25% to 8%–10%, attributed to the increased and early availability of SARS-CoV-2 testing, adherence to nonpharmaceutical interventions, development of novel treatments, and vaccination. Despite these positive steps, transplant programs and SOT recipients continue to face challenges. Vaccine efficacy in SOT recipients is substantially lower than the general population and SOT recipients remain at an increased risk of adverse outcomes if they develop COVID-19. SOT recipients and transplant teams need to remain vigilant and ongoing adherence to nonpharmaceutical interventions appears essential. In this review, we summarize the global impact of COVID-19 on transplant activity, donor evaluation, and patient outcomes over the past 2 y, discuss the current strategies aimed at preventing and treating SARS-CoV-2 infection in SOT recipients, and based on lessons learnt from this pandemic, propose steps the transplant community could consider as preparation for future pandemics.

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INTRODUCTION

The first reports of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), were made to the World Health Organization (WHO) on December 31, 2019. By March 11, 2020, COVID-19 had become a pandemic, and

within days, cases were reported in solid organ transplant (SOT) recipients.¹

Compared with COVID-19, previous pandemics have had minimal impact on global healthcare delivery systems in general and transplantation in particular.² The 2009 H1N1 pandemic resulted in high use of intensive care beds for patients with acute lung injury, with Argentina reporting a 50% reduction in organ donors during the disease peak,³ and during the 2003 SARS-CoV-1 epidemic, an outbreak in Toronto required transplant programs to be temporarily closed.⁴ These limitations, however, were localized and short lived, distinguishing them from the global repercussions of COVID-19.

The impact of COVID-19 on transplantation has varied geographically and over time. The past 2 y have seen national “lockdowns” and mandated nonpharmaceutical interventions to control spread of infection, with restrictions tightening and relaxing in line with “waves” of infection and the emergence of SARS-CoV-2 variants of concern.⁵ Effective treatments and vaccines have provided promise, but with the pandemic ongoing 2 y later, waitlisted patients, transplant recipients, and transplant programs continue to face unique challenges.

We discuss the impact of COVID-19 on global solid organ transplantation and review the current understanding of the outcomes, treatment, and vaccination against SARS-CoV-2 in SOT recipients.

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COVID-19 AND ORGAN DONATION AND TRANSPLANT ACTIVITY

Overview of Changes in Donation and Transplant Activity

At the start of the pandemic, the relative risks and benefits of transplantation in the context of COVID-19 were unknown, and early efforts were made to create risk prediction models to help determine the situations in which transplantation could continue versus being placed on hold.⁶ The concern of donor-derived disease transmission, adverse outcomes in immunosuppressed recipients, safety of living donors, and reduced availability of intensive care resources resulted in a widespread reduction in transplant activity, although varying approaches were taken by transplant centers within and between countries.⁷ A study of 22 countries comparing solid organ transplantation (SOT) rates in 2019 and 2020 estimated a 16% global decrease in transplant activity, most notable in the first 3 mo of the pandemic.⁸ However, substantial differences were noted between countries, with some experiencing large reductions in transplant activity despite low COVID-19 death rates (Argentina, Japan, Chile), others demonstrating a moderate fall in transplant rates with more sizable death rates (United Kingdom, France, Germany) and some showing a smaller decline in transplant rates despite high COVID-19 deaths (United States, Italy, Belgium).

Deceased Donor Transplantation

Reductions in transplant activity have been noted at all stages of the donation process, with most reports from early in the pandemic. First, reductions in donor referrals of 12%–39% were reported in 2020.^{9,10} National lockdowns and travel restrictions resulted in a reduction in major trauma and road traffic accidents,^{11,12} and in some locations, patients were hesitant to seek medical attention for other critical conditions—perhaps relating to fear of burdening already stretched healthcare systems or of contracting SARS-CoV-2 infection themselves.¹³ Intensive care units were caring for a different population, evidenced by a 4.5% reduction in donors dying from trauma, 25% reduction in donors dying from road traffic accidents, and 35% increase in donors dying from substance abuse over the first wave of the pandemic.¹⁴ Restrictions on acceptable donor criteria may have further limited organ referrals,⁹ and the strain on intensive care clinical teams could have reduced opportunities for broaching organ donation with families.¹⁵ Furthermore, it is not uncommon for potential donors to spend an additional 36–48 h in intensive care before donation. With bed, ventilator, and staff shortages, it is possible donor evaluation could not always be accommodated.¹⁶

Consent for donation has also varied. In France and the United States, consent fell by >10%,^{10,14} although the United Kingdom saw a rise in consent rates in the first half of 2020.⁹ Extended waiting times relating to delays in donor SARS-CoV-2 testing led to withdrawal of consent from some families.^{15,17,18} Furthermore, many hospitals had visiting restrictions meaning family discussions were held virtually, with prepandemic studies suggesting this associates with lower consent rates.¹⁹

A 20%–25% reduction in organ recovery was reported in the first wave of the pandemic,^{10,14,16,20,21} although regional variation was significant with some areas experiencing

reductions of 50%–80%.^{9,17,22} Furthermore, a US report of kidney transplantation found 21% of kidneys accepted for transplantation in 2020 were discarded, corresponding to COVID-19 surges and most frequently relating to the inability to locate an organ recipient.²³ A report from New York early in the pandemic also noted issues with organ allocation, finding organs were declined because of perceived infection risk despite negative donor SARS-CoV-2 swabs,²⁴ instead preferring local graft allocation to protect their teams and limit cold ischemic times given potential delays in organ transport because of reduced air travel.^{25,26}

Declines in deceased donor transplant rates varied by organ, over time, and with geographical location. In Italy, a 25% reduction in transplantation was reported in the first month of the pandemic¹⁶ and reductions of 50%–90% were reported in the United States, United Kingdom, Spain, France, and the Netherlands.^{9,15,17,27} The greatest reduction was in kidney transplantation, with a global decrease of 19% over 2020.⁸ Declines were seen in all organ types; heart transplantation was least impacted with a 5% global reduction in 2020.^{8,10,20,21,22,28,29}

Although geographical location influenced transplant activity, this was only partly explained by local COVID-19 rates,^{8,21,30} with some countries experiencing greater reductions in activity despite relatively low COVID-19 incidence and others maintaining a greater ability to transplant amid high infection.^{17,27} Country-level variation may reflect differences in critical care bed capacity,^{31–33} with UK deceased donation rates following an inverse relationship to COVID-occupied mechanical ventilation beds (Figure 1) and healthcare funding and delivery structures (Table 1). Furthermore, logistical challenges disrupted transplantation even in countries less impacted by COVID-19. For example, Australia enforced strict travel restrictions and border closures. Donation and transplantation services continued but faced barriers relating to the transportation of medical teams, organs, and patients.³⁴ Reduced commercial flights and quarantine requirements caused disruption, and at times, surgical teams were denied state entry for organ retrieval.³⁵ Therefore, although Australia experienced a relatively low incidence of COVID-19 in 2020/2021, reductions in kidney (27%), lung (12%), and liver transplant (8%) activity still occurred.³⁴

Changes in donor type have also been noted. Some centers altered acceptance criteria of deceased donors to protect intensive care beds and maximize the use of available organs. In the United Kingdom, the maximum age for donation after brainstem death and donation after circulatory death (DCD) donors was reduced from 85 to 60 y and 80 to 50 y, respectively, during the first wave.⁹ This was predicted to reduce number numbers by 47%, reduce nonproceeding offers from 18% to 12%³⁶ and increase the proportion of donation after brainstem death donors from 59% to 79%. Similar limitations to DCD age criteria were placed in Canada for liver transplant recipients,⁷ and reduced utilization of lower quality organs was noted in the United States.^{14,23} These practices result in the use of organs with a lower chance of delayed graft function, facilitating shorter hospital stays, and reduced likelihood of requiring critical care support.¹⁸ Countries with high use of DCD or extended criteria donors may therefore have been more significantly impacted. Conversely, centers that continued nonlocal organ utilization and did not limit donor criteria did not see such reductions in transplant

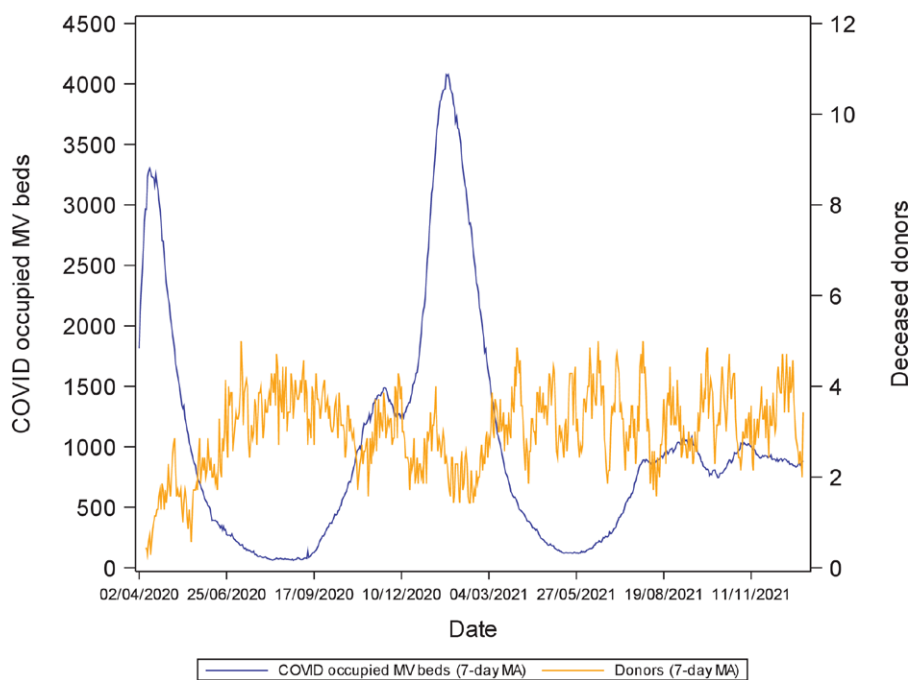


FIGURE 1. Deceased donor numbers in the United Kingdom (7-d MA) by MV bed occupancy by patients with COVID-19 (7-d MA) from April 2020 to December 2021. COVID-19, coronavirus disease 2019; MA, moving average; MV, mechanical ventilation.

activity, with 20% of US centers actually increasing their deceased donor transplant activity during the first wave of the pandemic and deceased donation in 2020 being 6% higher than 2019 in the United States.^{23,37}

Living Donor Transplantation

Living donor transplantation has experienced greater reductions in activity than deceased donor transplantation, with 2020 seeing a global 40% reduction in living donor kidney and 33% reduction in living donor liver transplantation, compared with an 11% reduction in deceased donor transplantation.⁸

Significant reductions or complete suspension of adult living donor transplant programs occurred early in the pandemic, with the greatest reductions in areas of high COVID-19 incidence.^{10,15,18,22,29,38,39} Reductions related to both donor and recipient concerns and administrative factors, such as loss of access to operating theaters, the need to create safe admissions pathways with designated staff for donors, and the redeployment of transplant teams.^{39,40} Potentially exposing “well” individuals who do not gain physical health benefits from donation to SARS-CoV-2 infection created ethical dilemmas, particularly when the risks of infection were poorly understood. Living donor

programs began to reopen after the first wave but were slow to restart even in areas where deceased donor transplantation continued.⁴¹

Recipient Selection for Transplantation During the Pandemic

Centers adopted differing approaches when selecting transplant candidates to remain active on the waiting list, based on the balance of risk of adverse COVID-19 outcomes and benefits of transplantation. Some centers restricted transplantation to their most complex patients, such as those with the most severe organ failure, limited dialysis access options, long waiting times, or high HLA sensitization.^{7,18,42,43} Others kept lower risk candidates active, such as those not requiring depleting induction therapy, no additional risk factors for severe COVID-19, and higher estimated posttransplant survival scores, who may be anticipated to require shorter hospital stays and be managed out with critical care.^{10,15,18,22,23}

Waiting List Activity

Waiting list registrations decreased in the early stages of the pandemic. In the United States, registrations fell by up to 50% in the first wave,²² and in France, reductions of 27% for lung, 15% for kidney, 10% for heart, and 2% for liver transplants were seen in 2020.¹⁰ Furthermore, wait-list suspensions were up to 75% higher than pre-pandemic levels, with 70% relating to COVID precautions, implying that center-level risks to service delivery or individualized risk assessment decisions at a patient-level necessitated suspensions.^{20,28} Globally, it is estimated 48 239 waitlisted patient life-years have been lost because of the pandemic.⁸

Transplant Activity in 2021

With time, the impact of COVID-19 on transplant activity has lessened though not been eliminated. Transplant

TABLE 1. Critical care beds and healthcare system by country

Country	Healthcare system	Critical care beds per 100 000 population
United Kingdom	Tax-based	6.6
Spain	Tax-based	9.7
France	Statutory health insurance	11.6
Italy	Tax-based	12.5
Germany	Statutory health insurance	29.2
United States	Health insurance	34.7

activity in 2021 has risen, with the most notable increases in living donor and kidney transplantation programmes,^{44,46} and deceased donor transplantation has generally continued during COVID-19 surges.³⁸ Prioritized SARS-CoV-2 testing for donors and recipients,⁴⁷ transporting organs instead of living donors,⁴⁸ the creation of “COVID-free” hospital pathways,⁴² and protection of transplant teams from redeployment¹⁰ are likely to have helped. Vaccination of donors, recipients, and transplant staff may also have played a role, with perceived protection from infection potentially lowering safety concerns and encouraging the reactivation of transplant candidates on the waitlist. Furthermore, the creation of collaborative networks to facilitate transfer of transplant activity to nearby centers in the event of local outbreaks have ensured patients’ need for transplantation is prioritized.⁴⁹ Ensuring availability of sufficient personal protective equipment, reducing acute bed pressures by opening off-site “field hospitals,” and recruiting additional staff are also likely to have increased centers’ resilience and ability to continue transplantation despite the challenges of COVID-19 surges.

With rising rates of COVID-19 at the end of 2021, there have been concerns of further limitations to organ donation and transplantation. The challenges in restarting transplant programs after suspensions in 2020 means greater emphasis has been placed on maintaining activity.⁴⁹ National transplantation authorities and societies have provided support and guidance to transplant centers to mitigate risk and ensure appropriate prioritization of transplantation.⁵⁰⁻⁵⁴

COVID-19 AND ORGAN DONORS

COVID-19 in Donors

SARS-CoV-2 is predominantly transmitted by airborne and droplet routes.⁵⁵ However, viral RNA has been found in hepatocytes, renal tubular cells, and the myocardium of critically ill patients and on postmortem, leading to concerns that donor-derived infection could occur.⁵⁶ Furthermore, the risk of contaminating operating theaters or exposing surgical teams to the virus resulted in initial hesitancy to accept SARS-CoV-2 positive donors.

Case studies have reported on the use of SARS-CoV-2 positive donors. Liver and kidney transplantation have been successfully performed.^{57,58} However, the risk appears greater for lung recipients, with at least 3 cases of donor-derived infection reported from donors with negative nasopharyngeal swabs but positive bronchoalveolar lavage samples at time of transplantation. One recipient died, although the nonlung recipients of organs from these donors remained well.^{59,60}

As of January 2022, guidelines continue to recommend caution with SARS-CoV-2 positive donors and avoiding lung transplantation, balancing the risks of transmission to the recipient and transplant team against the recipient’s risk of remaining on the waitlist.⁶⁰⁻⁶³ However, SARS-CoV-2 RNA positivity without other signs or symptoms of COVID-19 disease is not an absolute contraindication to transplantation, and RNA levels should be reviewed in detail to determine how infectious the donor is likely to be. The number of polymerase chain reaction amplification cycles needed to detect viral genetic material (the “cycle threshold”) reflects the viral load and can provide

information on the likelihood of there being transmissible live virus in the sample analyzed.^{64,65} There is no absolute cycle threshold that determines whether viable virus is present in the specimen, which varies depending on factors including the sample source, quality, assay used, and stage of infection. When interpreted in the correct context, however, the cycle threshold can provide useful information on the donor infectious status, with higher cycle thresholds associating with a lower likelihood of recovering viable virus. This can be seen in individuals who have recovered from SARS-CoV-2 infection, where SARS-CoV-2 RNA can be obtained for weeks or months in the absence of replicating virus in the respiratory sample. Given the complexity of these situations, input from clinical virologists or infection specialists is advisable.⁶⁶

For living donors, vaccination, social distancing, and a SARS-CoV-2 RNA test shortly before donation are advised.⁶⁰ If a donor contracts SARS-CoV-2 infection, recommendations are to consider avoiding surgery for 6–7 wks and ensure a negative RNA test before proceeding with donation.^{60,67} In India, which has a predominant living donor kidney transplant program, 31 transplants from donors who had recovered from COVID-19 were performed in 2020.⁴⁰ All donors had 2 negative RNA tests and symptom resolution for 28 d before surgery. No donor complications occurred, and there was 100% patient and graft survival. Living liver donation has also been reported 4 wks after infection in asymptomatic donors, again with no complications noted.⁶⁸

Donors With Vaccine-induced Thrombosis and Thrombocytopenia

In February 2021, concerns were raised over thrombotic events following SARS-CoV-2 vaccination by vaccine monitoring committees: a syndrome subsequently named vaccine-induced thrombosis and thrombocytopenia (VITT).⁶⁹ Cases were of cerebral venous sinus thrombosis associated with thrombocytopenia, raised D-dimer and antibodies against platelet factor 4 (anti-PF4), often in previously healthy individuals receiving the first dose of ChAdOx1 nCoV-19 (AstraZeneca) vaccine. The risk of VITT is higher in younger adults, and some countries have since implemented age restrictions for ChAdOx1.⁷⁰

The initial mortality following VITT was 25%–60%,^{71,72} and some affected individuals became organ donors. Studies from the United Kingdom, France, and Eurotransplant International Foundation described 19 donors proceeding to organ recovery.⁷³⁻⁷⁵ At least 2 livers were discarded preimplantation because of portal vein thrombosis and 1 lung required a thrombectomy, with 57 organs ultimately transplanted into 52 recipients. Follow-up times were short (1–2 mo). Four recipients experienced early graft failure requiring explants (3 livers and 1 kidney), and 1 recipient died of a presumed cardiac event. At least 3 recipients had bleeding episodes, and 6 experienced venous or arterial graft thrombosis. In the UK cohort, 3 of 13 recipients developed anti-PF4 antibodies.⁷³ No recipients in the French cohort developed anti-PF4 antibodies.⁷⁵

It is difficult to make definitive recommendations based on these small case series, but there seem to be risks of thrombosis or bleeding from donors with VITT, likely relating to preexisting graft endothelial dysfunction.⁷⁶

Monitoring of recipients' platelet count, fibrinogen, D-dimer, and anti-PF4 antibodies should be considered.⁷⁷ A low threshold for biopsy of organs from VITT donors is recommended to look for microvascular thrombosis before organ acceptance.⁷⁸ Given the greatest incidence in VITT is after the first vaccine dose, it is likely these cases will reduce with time.

COVID-19 IN TRANSPLANT RECIPIENTS

COVID-19 Outcomes

Outcomes in SOT Recipients

From the outset of the pandemic, there have been concerns about the risk of COVID-19 in SOT recipients, relating to their comorbid medical conditions, frequent contact with the healthcare system, and need for systemic immunosuppression. Although COVID-19 mortality has improved, relating to variations in access to testing, SARS-CoV-2 variants, effective treatments, and vaccination, SOT recipients remain at an increased risk of adverse outcomes compared with the general population and infection prevention remains key.⁷⁹

Factors associated with testing positive for SARS-CoV-2 include older age, non-White ethnicity, having a kidney transplant, being transplanted within the past year, and having a deceased donor as opposed to living donor organ, whereas liver transplant recipients have reduced infection risk.⁸⁰⁻⁸³ Further investigation is needed to determine if the ethnic variation with risk of contracting SARS-CoV-2 is confounded by socioeconomic status.

For SOT recipients testing positive for SARS-CoV-2, numerous studies have then examined their outcomes, as summarized in previous reviews.^{53,84} Many studies were from the first wave and frequently were either from single centers or relied on voluntary reporting of cases when access to testing was limited, resulting in variation in hospitalization and mortality rates. In the first wave, 75%–90% of SOT recipients with COVID-19 were hospitalized,⁸⁵⁻⁸⁷ a third required intensive care or mechanical ventilation,^{10,85,88-91} and crude mortality rates of 20%–25% were reported.^{80,85,88,90,92-94}

Over time, COVID-19 mortality has improved, although this is at least in part because of more widespread testing and differences in case mix reflecting greater capture of patients with less severe disease.⁹⁵ When examining hospitalized SOT recipients, in whom disease severity is presumed to be similar, US studies reported reductions in 28-d mortality from 20% to 25% in March–May 2020 to 14% in the latter part of 2020, with mortality remaining lower after adjustment for case mix.^{89,95} Similar reductions in mortality have been seen in Spain, falling from 26% to 17% over 2020.⁹⁶ Despite these improvements, the proportion of hospitalized SOT recipients requiring intensive care did not change over 2020, and in this most critically ill group mortality did not significantly improve.^{89,95-98} In addition to increased testing over time, the management of patients also evolved. Increased use of steroids occurred over 2020,^{95,96} and may also associate with improvements in outcomes.⁹⁹

Reports of COVID-19 mortality from 2021 examine the vaccinated population, with crude mortality rates of

around 10% in unvaccinated and 8% in vaccinated SOT recipients.^{100,101} Mortality varies by age, ranging from 2% to 3% in vaccinated individuals under 50 y, to 12%–17% in those >50 y depending on vaccination status and vaccine type, with a possible mortality benefit favoring ChAdOx1 over BNT162b2.¹⁰⁰ These outcomes predate the Omicron SARS-CoV-2 variant, the impact of which is still unknown in SOT recipients.

Risk factors for mortality among SOT recipients testing positive for SARS-CoV-2 include older age, cardiovascular and respiratory comorbidities, obesity, and biochemical parameters including lymphopenia, thrombocytopenia, and raised ferritin, C-reactive protein, troponin, or D-dimer.^{80,85,102} Lung transplant recipients seem to be at increased risk of mortality,^{96,100} as are those of Black ethnicity.¹⁰⁰ Although there is increased infection risk in patients transplanted more recently, no consistent association between transplant vintage and mortality has been observed,^{93,94,102,103} nor with immunosuppression regime (although immunosuppression does associate with immunological response to vaccination).

The earlier data highlight the impact of COVID-19 on SOT recipients. However, it must also be considered whether this reflects excess mortality among the SOT population, that is, whether overall mortality is greater than that from the prepandemic era. This has been illustrated by a registry analysis of the US kidney transplant population. Here, the 2020 death rate was 20% higher than in 2019, with 16% of deaths attributable to COVID-19. Recipients dying of COVID-19 were more likely to be younger, obese, of lower educational attainment and of an ethnic minority group than those dying of other causes. Furthermore, there were fewer non-COVID deaths in White recipients than previous years and almost no excess mortality in this group, contrasting with large numbers of excess deaths from COVID and non-COVID causes in Black and Hispanic recipients.¹⁰⁴

Outcomes in Waitlisted Patients

The risk of adverse outcomes among SOT recipients with COVID-19 has helped guide decision making on whether to continue transplantation through the pandemic. However, this must be balanced against the risk to patients on the waiting list.⁶ The risk benefit balance varies by transplant type, availability of other treatments for organ failure, and the risks associated with these treatments. This is particularly noteworthy for patients with kidney failure in whom dialysis is an option, providing an alternative to transplantation but often at the expense of frequent healthcare contact and reduced ability to socially distance.

The risk of SARS-CoV-2 infection in waitlisted patients is 2–3 times higher than that of SOT recipients, with the highest rates in kidney, kidney pancreas, and intestinal transplant candidates.^{80,103} Although there may be some bias in these estimates relating to testing practice, waitlisted patients are conceivably less able to distance resulting in an increased infection risk, and SARS-CoV-2 outbreaks in dialysis units have occurred.¹⁰⁵ COVID-19 mortality is lower among waitlisted patients than SOT recipients (10% versus 25% during the first wave), but the increased incidence results in comparable overall COVID-19 mortality between groups.^{80,81,103}

Again, the indirect effects of COVID-19 on waitlisted patients and excess mortality relating to cessation of transplant programs also needs considered. In a US study from March–May 2020, kidney transplant candidates had a 37% greater risk of all-cause mortality than prepandemic, although this finding was not replicated in other SOT candidates.¹⁰⁶ A US kidney transplant registry study found 11% of deaths on the waiting list related to COVID-19 in 2020 and overall waitlist mortality was 26% higher than in 2019.¹⁰⁴ These risks have tipped the balance in favor of continuing transplantation for most patients.

MANAGEMENT OF COVID-19: INFECTION PREVENTION

COVID-19 Vaccination

SARS-CoV-2 vaccines have been rapidly developed and mass vaccination programs began in December 2020. As of November 2021, 7 vaccines have WHO Emergency Use Listing, including the mRNA vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) and viral vector vaccines ChAdOx1 nCoV-19 (Oxford/AstraZeneca) and Ad26.COV2.S (Johnson & Johnson).¹⁰⁷ Primary vaccination courses comprise 2 doses except Ad26.COV2.S, which only requires 1 dose. In the general population, vaccine efficacy of 70%–95% is reported.¹⁰⁸

Most countries have adopted vaccination prioritization processes, including priority for SOT recipients.^{109–112} Uptake has generally been good, with 93% of SOT recipients double vaccinated by September 2021 in England,¹⁰⁰ and 80% receiving at least 1 dose by October 2021 in Italy.¹¹³ An international survey of SOT recipients in 2020 suggested 85% planned to accept vaccination,¹¹⁴ although uptake has varied by geographical location and ethnicity.¹¹⁵

Although SOT recipients are prioritized for vaccination, vaccine efficacy in this population was not tested before roll-out.^{116–119} SOT recipients mount lower immunological responses to vaccines than general populations,¹²⁰ and breakthrough infections were reported from early 2021.^{121,122} Multiple studies have since examined SOT recipients' immunological and clinical responses to vaccination.

Immunological Response to Vaccination

The threshold for protective immunity against SARS-CoV-2 is not known, with both antibody and T-cell responses being important. Anti-spike immunoglobulin G (IgG) concentration correlates with neutralizing capacity,^{123,124} and neutralizing capacity is predictive of immune protection.^{125,126} It should, however, be noted that the threshold for protection against severe infection is likely to be lower than that required to prevent infection.¹²⁷

After the first and second doses of SARS-CoV-2 vaccines, immunological responses are lower in SOT recipients than the general population (Table 2; Figure 2). After 1 dose, antibody responses were detected in just 6%–17% of SOT recipients with minimal neutralizing capacity,^{128–134} although cellular responses were more frequently observed in around 25% of patients.^{133,134} After a second dose, the proportion of recipients with antibody responses rises to 18%–64%, with neutralizing capacity in

two-thirds of these.^{131,132,135–145} Cellular responses are also higher, noted in 30%–79% of patients.^{133,134,140,142} Given T-cell responses can occur without detectable antibody responses, patients without antibodies could still mount a sufficient immune response to prevent severe infection. As such, the presence of antibodies should not be interpreted as indicating “immune protection” and routine antibody monitoring after vaccination is not universally recommended,¹⁴⁶ although it may still have a role in some circumstances, by determining eligibility for clinical trials and in assisting the prioritization of patients for treatments such as monoclonal antibodies.

Immunological response to vaccination varies by patient and transplant factors. The number and type of immunosuppressants appears important. Patients on mycophenolate mofetil (MMF)-containing regimes mount lower antibody responses than those not on MMF.^{128,129,136–138,141–145} This follows a dose dependent effect, with patients receiving under 1 g/d having a 5 times higher humoral response than patients on higher doses. Furthermore, following cessation of MMF, seroconversion has been noted in SOT recipients previously seronegative after 2 vaccine doses.¹⁴⁷ Patients receiving belatacept are also less likely to mount immunological responses.^{136,148,149} Other factors associated with reduced immunological responses include increased age,^{129,136,137,141,143} and lower kidney function, with every 1 mL/min/1.73m² increase in estimated glomerular filtration rate (eGFR) associating with a 3% increased likelihood of developing anti-spike IgG.^{128,136–138} Variation has also been observed with vaccine type. Humoral responses are more pronounced with mRNA-1273 than BNT162b2, and BNT162b2 than ChAdOx1,^{128,135,136} although cellular responses may be greater after viral vector vaccine priming. Heterologous second doses (ie, using a vaccine with a different mechanism of action) may also associate with greater immune responses.¹³⁴

The timing of vaccination in relation to transplantation is also likely to be important. Patients with a longer duration of transplantation have better immunological responses than recipients transplanted more recently, particularly within the past year.^{129,133,135,136,142,143} Response to vaccination is also greater in patients on dialysis or the liver transplant waiting list than SOT recipients, with 80%–95% having antibodies after 2 doses in addition to greater T-cell responses, suggesting vaccination before transplantation is likely to be beneficial.^{133,136,150–152} Early reports of kidney transplant recipients who were vaccinated pretransplantation show seroconversion is sustained posttransplantation.¹⁵³

Clinical Responses

Although immunological responses to standard vaccine regimes in SOT recipients may be disappointing, vaccination still improves some clinical outcomes. By April 2021, breakthrough infection had occurred in 0.83% of vaccinated SOT recipients in the United States,^{101,154} and by October 2021 in Scotland breakthrough infection occurred in 8% of kidney transplant recipients, with infection being more frequent in those of younger age or from areas of deprivation.¹⁵⁵ These breakthrough rates are greater than in the general population,^{79,156} and a national registry study in England found that vaccination does not reduce the

TABLE 2.
Studies examining immunological responses to first and second doses of a COVID-19 vaccine

Author	Population	Vaccine	Dose	Measured response	Time postvaccine	Proportion with response	Associations with reduced response
Boyarsky et al ¹²⁸	436 SOT recipients	BNT162b2 mRNA-1273	First	Anti-spike IgG	20 d	17%	Antimetabolite Increased age BNT162b2 vaccine
Benotmane et al ¹²⁹	242 kidney transplant recipients	mRNA-1273	First	Anti-spike IgG	28 d	10.8%	Shorter time from transplant Use of MMF Use of steroids Higher creatinine
Yi et al ¹³⁰	145 kidney transplant recipients	BNT162b2M mRNA-1273	First	Anti-spike IgG	At second dose	5.5%	Not examined
Boyarsky et al ¹³¹	658 SOT recipients	mRNA-1273	First	Anti-spike IgG	21–29 d	Dose 1: 15% Dose 2: 54%	Not examined
Marion et al ¹³²	895 first dose, 367 second dose SOT recipients	BNT162b2M mRNA-1273	First Second	Anti-spike IgG	28 d	Dose 1: 6.4% Dose 2: 33.8%	Not examined
Bertrand et al ¹³³	45 kidney transplant recipients	BNT162b2	First Second	Anti-spike IgG IFN- γ producing T cells	21–28 d	Dose 1: 2.2% humoral 24.4% cellular Dose 2: 17.8% humoral 57.8% cellular	Humoral response: Recent transplantation Immunosuppression regime Cellular response: No significant association
Schmidt et al ¹³⁴	40 SOT recipients	BNT162b2M mRNA-1273 ChAdOx1	First Second	Anti-spike IgG Neutralizing capacity IFN- γ producing T cells		Dose 1: 5.3% humoral 23.7% cellular 26.3% humoral or cellular Dose 2: 35.3% humoral 64.7% cellular 70.6% humoral or cellular	Homologous vaccine regime
Prendecki et al ¹³⁵	920 kidney transplant recipients	BNT162b2 ChAdOx1	Second	Anti-spike IgG T-cell response to spike protein	31 d	55% humoral 11% cellular 58% humoral or cellular	Humoral response: ChAdOx1 vaccine Transplantation within 1 y Diabetes
Stumpf et al ¹³⁶	368 kidney transplant recipients	BNT162b2 mRNA-1273	Second	Anti-spike IgG/IgA Neutralizing capacity IFN- γ producing T cells	28–35 d	42% humoral response 66% with neutralizing capacity 30% cellular response	Use of MMF Use of CNI Use of belatacept BNT162b2 vaccine Older age Shorter duration of transplant
Rozen-Zvi et al ¹³⁷	308 kidney transplant recipients	BNT162b2	Second	Anti-spike IgG	28 d	36.4%	Higher MMF dose Higher CNI levels Lower eGFR Older age
Kantauskaite et al ¹³⁸	225 kidney transplant recipients	BNT162b2 mRNA-1273	Second	Anti-spike IgG Neutralizing capacity	14 d	24.9% 68% with neutralizing capacity	Higher trough MMF concentration Lower eGFR
Benotmane et al ¹³⁹	205 kidney transplant recipients	mRNA-1273	Second	Anti-spike IgG	28 d	47.8%	Previous kidney transplant Shorter transplant duration Lower eGFR More immunosuppression

Continued next page

TABLE 2. (Continued)

Author	Population	Vaccine	Dose	Measured response	Time postvaccine	Proportion with response	Associations with reduced response
Cucchiari et al ¹⁴⁰	148 kidney and kidney pancreas recipients	mRNA-1273	Second	Anti-spike IgG/M IFN- γ producing T cells	14 d	29.9% humoral 54.7% cellular 65% humoral or cellular	Humoral response: Immunosuppression regime Cellular response: Diabetes Lymphopenia Decreasing eGFR ATG within 1 y
Grupper et al ¹⁴¹	136 kidney transplant recipients	BNT162b2	Second	Anti-spike IgG	16.5 d	37.5%	Older age High dose steroid in past y Triple immunosuppression Use of MMF
Herrera et al ¹⁴²	104 liver and heart transplant recipients	mRNA-1273	Second	Anti-spike IgG IFN- γ producing T cells	28 d	64% humoral 79% cellular 90% humoral or cellular	Humoral response: Hypogammaglobulinemia Transplant within 1 y Higher dose of MMF Cellular response: Hypogammaglobulinemia
Rabinowich et al ¹⁴³	80 liver transplant recipients	BNT162b2	Second	Anti-spike IgG	14.8 d	47.5%	Older age High dose steroid in past y Use of MMF Triple immunosuppression Lower eGFR Use of MMF
Peled et al ¹⁴⁴	77 heart transplant recipients	BNT162b2	Second	Anti-RBD IgG Neutralizing antibody	21 d	18% 57% with neutralizing capacity	Use of MMF
Marinaki et al ¹⁴⁵	34 SOT recipients	BNT162b2	Second	Anti-spike IgG	10 d	58.8%	Use of MMF

This represents merely a selection of studies and is not an exhaustive list.

ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; IFN- γ , interferon gamma; Ig, immunoglobulin; MMF, mycophenolate mofetil; RBD, receptor-binding domain; SOT, solid organ transplant.

risk of testing positive for SARS-CoV-2 in SOT recipients. Infection was in fact more frequent in vaccinated recipients (incidence rate ratio, 1.29; 95% confidence intervals [CI], 1.03-1.61), hypothesized to relate to risk compensation behavior in vaccinated individuals.¹⁵⁷ Of SOT recipients testing positive for SARS-CoV-2, vaccination associated with a 20% reduction in risk of death (8.2% versus

10.4%), but this was driven by a 30% mortality reduction in those receiving ChAdOx1 (hazard ratio, 0.69; 95% CI, 0.52-0.92), whereas BNT162b2 did not confer mortality benefit (hazard ratio, 0.97; 95% CI, 0.71-1.31).¹⁰⁰ In Scotland, vaccine effectiveness of 40% at preventing infection and hospitalization has been being reported in kidney transplant recipients,¹⁵⁵ lower than the 70%–90% vaccine

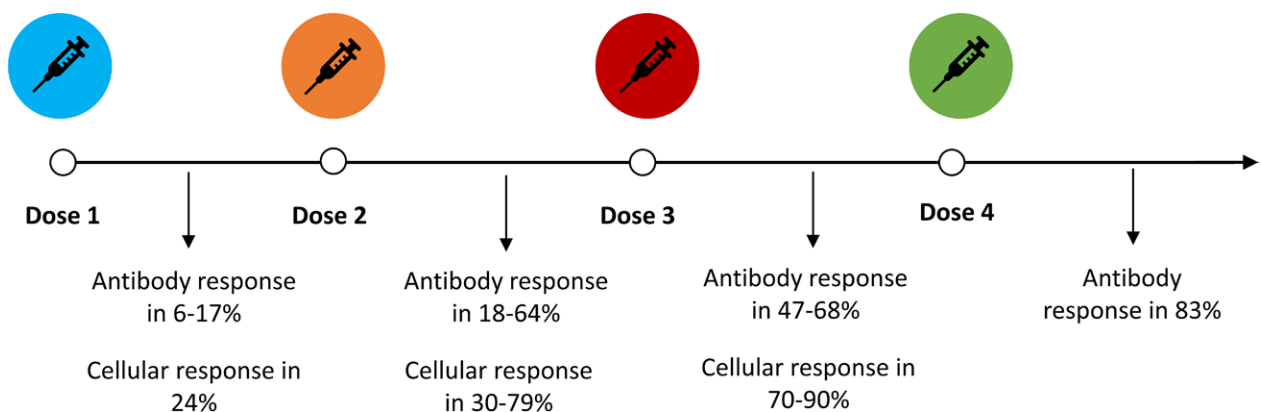


FIGURE 2. Immunological responses to severe acute respiratory syndrome coronavirus 2 vaccination doses in solid organ transplant recipients. References for this figure are taken from studies within Tables 2 and 3.

effectiveness in general populations.¹⁵⁸⁻¹⁶⁰ These findings highlight the importance of additional protective measures in SOT recipients such as further vaccine doses, use of novel antivirals and monoclonal antibodies, and ongoing adherence to nonpharmaceutical interventions such as face masks and social distancing.

Repeated Doses

The reduced immunological and clinical responses to vaccination in SOT recipients have led to the investigation of third vaccine doses (Table 3; Figure 2). A randomized control trial of the mRNA-1273 vaccine found that a third dose 2 mo after the primary vaccine course resulted in a significant rise in the proportion of SOT recipients with detectable antispikes IgG (55% versus 18%) and an increase in SARS-CoV-2 reactive T cells.¹⁶¹ Nonrandomized studies have similarly shown improvements in antibody and T-cell responses after a third dose, including improved serum neutralizing capacity and rises in antibody titers in previously seropositive patients. Between 30% and 50% of seronegative SOT recipients after 2 doses seroconverted

after a third dose.^{162,163,164,165-168} However, by 6 mo postvaccination immunological responses can wane,¹⁶⁹ with a 64% reduction in antibody titer and 62% reduction in T-cell activity being reported in kidney transplant recipients.¹⁷⁰

Clinical outcomes in SOT recipients following third vaccine doses are not yet reported. In general populations, the risk of SARS-CoV-2 infection starts to rise from 90 d postvaccination,¹⁷¹ and third doses associate with a reduced risk of infection and mortality.^{172,173} In dialysis patients, 3 vaccine doses are required to protect against infection from the Omicron SARS-CoV-2 variant, although similar studies in SOT recipients are awaited.¹⁷⁴

Based on current evidence, 3 vaccine doses are now frequently recommended as a “primary course” for SOT recipients, followed by a fourth “booster” dose.^{175,176} A small case series of SOT recipients receiving a fourth dose found 63% of those with negative or low-positive antibody titers after 3 doses developed high titer responses after dose 4.¹⁷⁷

TABLE 3.

Immunological responses to third dose of a COVID-19 vaccine

Author	Population	Vaccine	Measured response	Time postvaccine	Response rate	Associations reduced response
Del Bello et al ¹⁶²	396 SOT recipients	BNT162b2	Anti-spike IgG	28 d	5.1% after first dose, 41.4% after second dose, 67.9% after third dose 45% seronegative patients after second dose seroconverted after third dose	Older age Use of MMF Use of belatacept
Benotmane et al ¹⁶³	159 kidney transplant recipients	mRNA-1273	Anti-spike IgG	28 d	Only examined patients with no significant response to 2 vaccine doses 49% seroconverted after third dose	Triple agent immune suppression
Kamar et al ¹⁶⁴	101 SOT recipients	BNT162b2	Anti-spike IgG	28 d	40% after 2 doses to 68% after third dose 44% seronegative patients after second dose seroconverted after third dose	Increased age Lower eGFR
Bertrand et al ¹⁶⁵	80 kidney transplant recipients	BNT162b2	Anti-spike IgG IFN- γ producing spike-reactive T cells	Minimum 4 wks	Humoral response: 37.5% after second dose to 61.2% after third dose Cellular response: 51.2% after second dose to 70% after third dose	Use of belatacept Use of MMF
Massa et al ¹⁶⁶	61 kidney transplant recipients	BNT162b2	Anti-spike IgG Neutralizing capacity IFN- γ producing spike-reactive T cells	28 d	44.3% after second dose to 62.3% after third dose One-third seronegative patients after second dose seroconverted after third dose Increase in neutralizing capacity after third dose Rise in frequency of spike-reactive T cells	Use of antiproliferative Lymphopenia
Werbel et al ¹⁶⁷	30 SOT recipients	BNT162b2 mRNA-1273	Anti-spike IgG	60 d (second dose), 14 d (third dose)	20% after second dose to 47% after third dose One-third seronegative patients after second dose seroconverted after third dose	Not examined
Schrezenmeier et al ¹⁶⁸	25 kidney transplant recipients	BNT162b2 ChAdOx1	Anti-spike IgG/IgA CD4 T-cell reactivity to spike peptide mix	7–28 d	36% seronegative patients after second dose seroconverted after third dose; 28% after homologous and 45% after heterologous vaccination Spike-specific CD4 T-cell responses in over 90% after the second and third dose	Not examined

Vaccination Strategies

Based on the earlier evidence, vaccination of transplant candidates and recipients is strongly recommended in transplant guidelines, with vaccination occurring pre-transplantation if possible.^{146,178} The optimum vaccine timing posttransplantation is unknown, although most guidelines suggest waiting for 1–3 mo to optimize vaccine responses.^{179–181}

For transplant candidates who decline vaccination, there are ethical issues surrounding transplantation.¹⁸² The risks to the patient, their graft, transplant programs, and society need to be considered but must be balanced against autonomy and justice. Clinicians should discuss vaccination with patients, although most suggest declining vaccination not be an absolute contraindication to transplantation.¹⁸³

Given the reduced responsiveness to vaccination in SOT recipients, additional doses, “ring immunization” (prioritizing household members and caregivers for vaccines), and mandatory vaccination of healthcare staff is being considered in some countries.¹⁸⁴ Although the optimum vaccination strategy is waiting to be determined, continued adherence to nonpharmaceutical interventions is an advisable supporting strategy.

Nonvaccine Prophylaxis Against COVID-19

There is some evidence to support addition nonvaccination treatments to prevent COVID-19. The receipt of the SARS-CoV-2 monoclonal antibody casirivimab plus imdevimab after a household exposure to COVID-19 associated with a 66% relative risk reduction of developing infection and faster resolution of symptoms in clinical trials predating the emergence of the Omicron variant¹⁸⁵ and is licensed in the United States for individuals at high risk of severe disease who are a close contact of a positive case.¹⁸⁶ Casirivimab plus imdevimab, however, does not maintain efficacy against Omicron, and currently there are no authorized treatments with anti-Omicron activity for postexposure prophylaxis. The United States has emergency use authorization for the long-acting monoclonal antibody tixagevimab plus cilgavimab as preexposure prophylaxis in immunocompromised individuals,¹⁸⁷

although the evidence for this also predates the Omicron variant.¹⁸⁸ Results are awaited from further studies on novel prophylactic treatments in SOT recipients without SARS-CoV-2 exposure.^{187,189,190}

MANAGEMENT OF COVID-19: TREATMENT OF SARS-COV-2 INFECTION

There are >5000 registered randomized control trials of treatments for COVID-19, and this field is changing rapidly. The below summarizes evidence as of December 2021. Living meta-analyses, such as those by the MAGIC Evidence Ecosystem Foundation (www.magicproject.org), provide up-to-date information. Current management of COVID-19 is illustrated in Figure 3.

Treatment of Patients With Nonsevere COVID-19

For patients with nonsevere COVID-19 managed in the community, studies suggest no benefit to azithromycin,¹⁹¹ doxycycline,¹⁹² and colchicine,¹⁹³ and although inhaled corticosteroids may reduce symptom duration in older patients or those with comorbidities, their effect on hospitalization and mortality is less clear.¹⁹⁴

In patients with risk factors for severe COVID-19, such as SOT recipients, monoclonal antibodies against the SARS-CoV-2 spike protein have shown potential in randomized controlled trials. Casirivimab plus imdevimab reduces hospitalization or death by 70% and shortens symptoms by 4 d.¹⁹⁵ Sotrovimab administered within 5 d of symptom onset is associated with an 85% relative risk reduction of hospitalization or death at 1 mo (1% treatment group versus 7% placebo group) in a prespecified interim analysis,¹⁹⁶ with positive outcomes predominantly driven by reductions in hospitalization.¹⁹⁷ Similar outcomes to these large studies have been reported in small series of SOT recipients.^{198,199} It should be noted that these studies were performed before the emergence Omicron variant and before vaccination, although case reports of vaccinated SOT recipients infected with the Alpha, Delta, and Gamma variants suggest monoclonal antibodies could still be beneficial.²⁰⁰ Furthermore, casirivimab plus imdevimab is less effective against the Omicron variant,

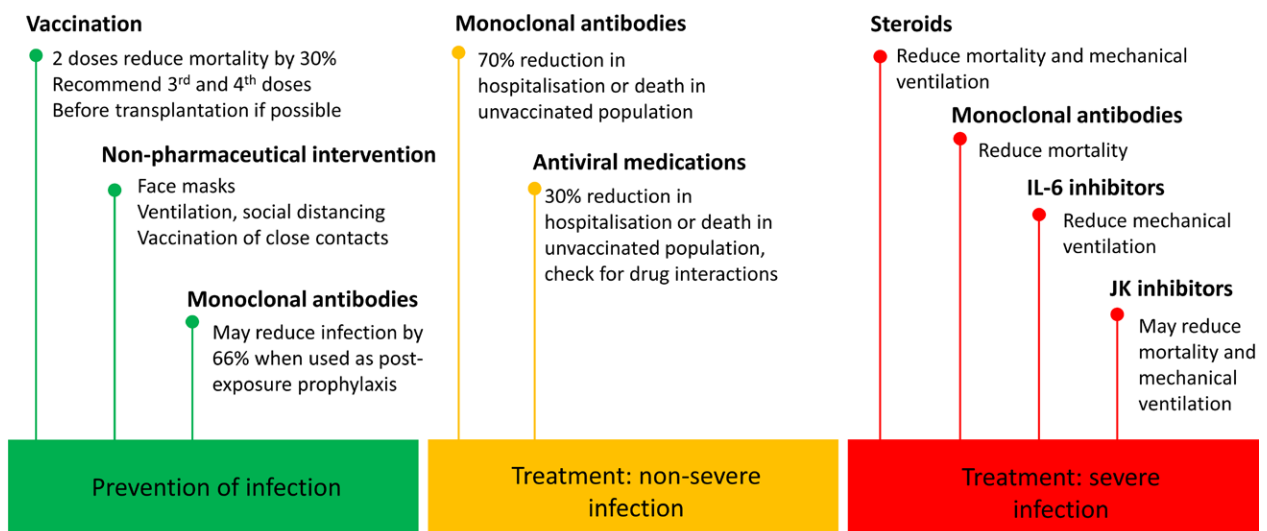


FIGURE 3. Strategies for preventing and treating severe acute respiratory syndrome coronavirus 2 infection in solid organ transplant recipients. References for this figure are quoted within the main text of the article. IL, interleukin; JK, Janus kinase.

and given sotrovimab has greater proposed efficacy treatment choices may need to reflect the dominant SARS-CoV-2 variant.²⁰¹ Finally, monoclonal antibodies are currently given as an intravenous or subcutaneous infusion, so pathways to facilitate their administration safely to ambulatory patients are needed. Intramuscular sotrovimab is reported to offer similar efficacy to intravenous formulations and, if confirmed, could expand delivery options and improve access to treatment.²⁰²

The oral antiviral drug molnupiravir, a competitive nucleoside analogue in RNA dependent RNA polymerase, has also shown promise in nonhospitalized patients at risk of severe COVID-19. An interim analysis of 775 patients in the MOVE-OUT study suggested a 45% reduction in hospitalization or death,²⁰³ although the full cohort analysis in 1433 patients showed a more modest relative risk reduction of 30%, with 6.8% of patients receiving molnupiravir dying or requiring hospitalization versus 9.7% in the control arm.²⁰⁴ Again, studies were performed before vaccination and patients with an eGFR < 30 mL/min/1.73m² were excluded, although molnupiravir is not renally excreted and benefits in patients with renal dysfunction likely outweigh risks. Immunosuppressant drug interactions are not expected, although molnupiravir is teratogenic and contraceptive advice is required.

Other antiviral drugs also show promise. An interim analysis of the oral antiviral ritonavir-nirmatrelvir suggests an 89% reduction in hospitalization or death if taken within 3 d of symptoms in individuals at risk of severe disease and has been approved for use in the United Kingdom and United States.²⁰⁵ Ritonavir, however, is a CYP-450 inhibitor and interacts with calcineurin and mammalian target of rapamycin inhibitors, requiring dose reductions and close drug level monitoring.²⁰⁶ Careful supervision by experienced transplant professionals appears sensible, whilst studies of its safety in SOT recipients are awaited. Furthermore, results from the PINETREE study published in January 2022 show a 3-d course of intravenous remdesivir in patients at risk of severe COVID-19 reduces hospitalization or death by 87%, although again would require establishment of safe pathways to facilitate its administration to outpatients.²⁰⁷

Treatment of Patients With Moderate to Severe COVID-19

The WHO Guideline Development Group living systematic review and meta-analysis evaluates treatments with sufficient evidence on which to make recommendations.²⁰⁸ In general populations, for patients with severe disease (oxygen saturation < 90%, respiratory distress, or organ support), current evidence is in favor of:

- Steroids (eg, dexamethasone): these reduce death (odds ratio [OR], 0.83; 95% credible interval [CrI], 0.69-0.98, moderate certainty) and mechanical ventilation (OR, 0.76; 95% CrI, 0.59-0.99, moderate certainty).
- Interleukin-6 inhibitors (eg, tocilizumab, sarilumab): these reduce mechanical ventilation (OR, 0.72; 95% CrI, 0.57-0.90, moderate certainty) and length of hospital stay (-4.5 d; 95% CrI, -6.7 to -2.3) but have an uncertain effect on mortality (OR, 0.87; 95% CrI, 0.74-1.05, low certainty). Case series of tocilizumab in SOT recipients suggest it is safe to use.^{209,210}

- Monoclonal antibodies against SARS-CoV-2 (eg, casirivimab plus imdevimab, sotrovimab): these reduce mortality in patients seronegative at diagnosis.²¹¹
- Janus kinase inhibitors (eg, baricitinib, ruxolitinib): these are targeted synthetic disease modifying antirheumatic drugs that interfere with cytokine signaling pathways. These may reduce mortality (OR, 0.58; 95% CrI, 0.33-1.00) and mechanical ventilation (OR, 0.57; 95% CrI, 0.33-0.95), although the certainty of benefit is low.

Recommendations are currently against the use of hydroxychloroquine, azithromycin, interferon-beta, ivermectin, lopinavir-ritonavir, and convalescent plasma (unless in a clinical trial) given a lack of clinically significant effects on outcomes.²⁰⁸ The antiviral remdesivir had initial positive reports, but meta-analysis shows no difference in mortality (OR, 0.90; 95% CI, 0.70-1.12) or mechanical ventilation (OR, 0.89; 95% CI, 0.76-1.03) based on low certainty evidence, resulting in a weak recommendation against its use from WHO.²⁰⁸ Despite this, remdesivir continues to be recommended under specific circumstances in other clinical practice guidelines,²¹² and more data are needed on its use in SOT recipients in whom its effect on outcomes may differ compared with the general population.

Immunosuppression Management

There is no robust evidence to guide the management of immunosuppression in the context of COVID-19, though minimization of immunosuppression is common with other viral infections.²¹³ However, given many of the severe manifestations of COVID-19 relate to release of proinflammatory cytokines,²¹⁴ the balance of immunosuppression in the setting of COVID-19 is complex.²¹⁵

At present, preemptively reducing maintenance immunosuppression in SOT recipients without COVID-19 to reduce the risk of acquiring infection, progression to severe disease, or improve vaccine responses has not generally been recommended, partly because of concerns over reduced ability to follow up patients during COVID-19 surges.²¹⁶ In those testing positive for SARS-CoV-2, a stepwise reduction of immunosuppression is usually performed. This typically starts with the antimetabolite, with MMF being reduced or stopped. Further reductions are suggested in patients with severe disease, although there is no comparative data to guide recommendations and decisions should be based on individualized assessment of the severity of COVID-19 and consequences of rejection.²¹⁷⁻²²⁰

PSYCHOLOGICAL IMPACT OF THE PANDEMIC ON PATIENTS AND STAFF

The impact of the pandemic on individuals cannot be fully captured by outcomes such as mortality risk. Severe isolation from nonhousehold contacts, media reminders of their “high risk” status, and changes in access to healthcare are likely to influence patients’ wellbeing. Generally, SOT recipients have shown remarkable resilience, with many adopting positive coping strategies such as acceptance, self-distraction, and positive reframing, which they may have developed through their experience of living with organ failure.²²¹ SOT recipients also noted that transplantation increased their attention to hygiene and infection prevention strategies.²²² Despite this, half of kidney

TABLE 4.**Suggested recommendations to transplant teams for research priorities for the SARS-CoV-2 pandemic, and planning and preparedness for future pandemics**

Research priorities for the SARS-CoV-2 pandemic	<ul style="list-style-type: none"> • Assess safety of use of SARS-CoV-2–positive donors. • Determine optimal vaccination regime for SOT recipients. • Determine efficacy of novel treatments in a vaccinated population. • Assess potential demand and indications for lung transplantation for post–COVID-19 pulmonary fibrosis. • Prioritize methods to maintain wellbeing of transplant teams.
Planning and preparedness for future pandemics	<ul style="list-style-type: none"> • Early assessment and consensus derivation on the likelihood of donor-derived infection transmission for example, based on plausibility of blood borne or respiratory transmission. • Advocacy for rapid nucleic acid testing of potential organ donors and recipients. • Early identification of resources that allow safe continuation of transplant programs without overlap with resources caring for patients with active infection, for example, ring-fenced transplant unit and intensive care beds and operating theaters. • Development of risk prediction tools/calculators that utilize simulation and machine-learning approaches to assist in decision making by transplant centers. • Advocacy for SOT recipients to be included in clinical trials of novel vaccines and antiviral treatments or clinical trials exploring novel or repurposed treatments. • Establish national and international registry linkages to enable real-time assessment of infection and mortality risk in SOT recipients and waitlisted patients. • Establish infrastructure for organ donation and transplant organizations from across the world to collaborate as a consortium to rapidly derive clinical and patient facing consensus guidance.

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant.

transplant recipients worried more about their health and a third wanted to postpone hospital appointments to minimize their risk of COVID-19,^{222,223} noting the benefits of telehealth.²²⁴

For patients on the waiting list, the suspension of transplant programs left some feeling disappointed and helpless with concerns their health could deteriorate.²²⁵ Although most patients were in favor of waiting list reactivation, this was not universal, highlighting the need for individualized discussions as the pandemic picture evolves.²²⁶

The impact of pandemic-working on the transplant multidisciplinary teams should also be noted. Burnout has been described in half of nephrology and hepatology workforces during the pandemic,^{227,228} and rates may be higher in intensive care environments.²²⁹ The wellbeing of staff is key to protect transplantation programs and patients, with strategies including flexible working and optimizing staffing levels being recommended.²³⁰

CONCLUSIONS

Huge advances in the management of COVID-19 have been made during the second year of the pandemic. Transplantation rates are returning to prepandemic levels, novel treatments have been identified, and vaccination of SOT recipients has been prioritized. However, further challenges are likely, emphasized by the recent rapid spread of the Omicron variant, the impact of which is unknown at the time of writing.

Important lessons have been learnt from the pandemic. Rapid research approvals, public engagement in clinical trials, streamlined registry data linkages, preprint articles and expedited publication of open-access papers have helped rapidly disseminate new knowledge. Collaborative working of transplant teams at regional, national, and international levels, and examples of strong leadership to support staff and patients have been seen. The exclusion of

immunosuppressed patients from vaccine trials has, however, delayed our understanding of vaccine effectiveness in a vulnerable population in whom disease prevention is key. In the future, including such individuals in sub-studies could help inform clinical and policy decisions. Other suggested strategies to transplant teams to mitigate avoidable risks for patients in a future pandemic are shown in Table 4.

The COVID-19 pandemic is likely to move to an endemic phase, with vaccination reducing COVID-19 mortality but potentially not infection rates in SOT recipients. In the event of ongoing cases, the optimal strategies for prevention and treatment of COVID-19 must be identified, and the safety of using organs from SARS-CoV-2 positive donors considered. Furthermore, it remains to be seen how transplantation will be affected as the pandemic wanes, for example whether post–COVID-19 pulmonary fibrosis will increase demand for lung transplantation.^{231,232} As a return to normality occurs for general populations, many SOT recipients still have concerns over their protection from SARS-CoV-2, and nonpharmaceutical precautions may still be advisable.

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