



Immune Responses to SARS-CoV-2 in Solid Organ Transplant Recipients

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Abstract

Purpose of Review Coronavirus disease 2019 (COVID-19) is caused by a complex interplay between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) dynamics and host immune responses. Hosts with altered immunity, including solid organ transplant recipients, may be at increased risk of complications and death due to COVID-19. A synthesis of the available data on immune responses to SARS-CoV-2 infection is needed to inform therapeutic and preventative strategies in this special population.

Recent Findings Few studies have directly compared immune responses to SARS-CoV-2 between transplant recipients and the general population. Like non-transplant patients, transplant recipients mount an exuberant inflammatory response following initial SARS-CoV-2 infection, with IL-6 levels correlating with disease severity in some, but not all studies. Transplant recipients display anti-SARS-CoV-2 antibodies and activated B cells in a time frame and magnitude similar to non-transplant patients—limited data suggest these antibodies can be detected within 15 days of symptom onset and may be durable for several months. CD4⁺ and CD8⁺ T lymphopenia, a hallmark of COVID-19, is more profound in transplant recipients, but SARS-CoV-2-reactive T cells can be detected among patients with both mild and severe disease.

Summary The limited available data indicate that immune responses to SARS-CoV-2 are similar between transplant recipients and the general population, but no studies have been sufficiently comprehensive to understand nuances between organ types or level of immunosuppression to meaningfully inform individualized therapeutic decisions. The ongoing pandemic provides an opportunity to generate higher-quality data to support rational treatment and vaccination strategies in this population.

Keywords SARS-CoV-2 · COVID-19 · Solid organ transplant · Immune response · Vaccine

Introduction

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), results from a complex interplay between viral dynamics and host immune responses [1]. Most of the end-organ complications that characterize severe COVID-19 are attributable to a dysregulated immune response that follows from SARS-CoV-2 infection. As a result, there has been intense interest in identifying immunomodulatory therapeutics that may alter the clinical course and outcome of SARS-CoV-2 infection and prevent or mitigate severe COVID-19.

Despite the growing evidence base for various immunomodulatory therapies, there is a relative paucity of high-quality data on the impact of chronic immunosuppressive therapy on the immune response to SARS-CoV-2 infection. The cumulative observational evidence suggests that some hosts with altered immunity—including solid organ transplant

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(SOT) recipients—may be at elevated risk of complications and death due to SARS-CoV-2 infection [2–7]. Conversely, intensity of immunosuppression—as assessed by time since transplant, type of transplant, number of immunosuppressive agents, or recent augmented immunosuppression—was not associated with COVID-19 severity in one large multicenter series [5]. In more recent comparative studies, clinical outcomes between transplant recipients and non-transplant patients appear to be similar when using carefully matched cohorts [8, 9]; in one such analysis, transplant recipients exhibited faster clinical improvement [10]. As a result of these conflicting observations, the approach to the management of chronic immunosuppressive therapy in SOT recipients with COVID-19 has largely been extrapolated from experience with other viral pathogens, not on a detailed understanding or profiling of the immune response to SARS-CoV-2 in the SOT population.

Given the ongoing nature of the COVID-19 pandemic and the burden of severe disease in immunocompromised hosts, a comprehensive understanding of how immune responses to SARS-CoV-2 vary in hosts with altered immunity—including specifically SOT recipients—is needed to provide a basis for therapeutic and preventative strategies in this patient population. In this review, we synthesize and provide context to the available data on immune responses to human and zoonotic coronaviruses, with a focus on SARS-CoV-2, in SOT recipients. We also discuss the implications of these findings, as well as evidence from studies of other pathogens, for SARS-CoV-2 vaccination in this patient population and outline potential avenues for future research.

Immune Response to SARS-CoV-2 in Non-transplant Patients

The immune response to SARS-CoV-2 in non-transplant patients has been reviewed extensively elsewhere [1, 11, 12]. Following SARS-CoV-2 infection of airway epithelial cells, numerous pro- and anti-inflammatory cytokines (IL-1 β , IL-2, IL-6, IL-10, IFN- γ , IP-10, macrophage inflammatory protein 1 α (MIP1 α), MIP1 β , and MCP1) are elaborated [13]. In patients with mild-moderate disease, this inflammatory cascade results in recruitment of monocytes, macrophages, Th1-biased CD4⁺ T cells, and generation of anti-SARS-CoV-2-neutralizing antibodies [14] as well as broadly reactive CD4⁺ and CD8⁺ T cells (with spike as the dominant epitope) [15, 16], and these effectors together act to limit viral replication and halt disease progression. Based on longitudinal studies of adaptive immune responses in non-transplant patients, these neutralizing antibodies and SARS-CoV-2-reactive T cells can persist for at least 8 months after initial infection and likely contribute to protection against reinfection [17–19].

In contrast, in patients that develop severe (and often fatal) COVID-19, viral replication goes unchecked and the immune response becomes dysregulated resulting in a “cytokine storm” that leads to vascular leak, acute lung injury and acute respiratory distress syndrome (ARDS), sepsis, thrombotic complications, and multiorgan failure. Systematic immune profiling of patients with mild and severe COVID-19 has identified a distinct immune “phenotype” associated with more severe disease [20, 21]. This includes persistently elevated and rising levels of pro-inflammatory cytokines such as IL-6 [13, 22], higher levels of anti-SARS-CoV-2 antibodies [22, 23] (which have also been associated with multisystem inflammatory syndrome in children (MIS-C) [24]), and more profound T cell depletion (and in some studies, exhaustion) [20]. Additionally, immune profiling studies suggest a dichotomous response in patients with severe COVID-19, with immune activation in the lung and blunted responses in the systemic circulation [21, 25].

This over-exuberant immune response is the target of various immunomodulatory therapies that have been proven or are under investigation for the treatment of COVID-19. Early in the pandemic, corticosteroids were identified as providing a mortality benefit to patients with moderate-severe disease [26, 27], and dexamethasone is now standard of care for such patients. In a randomized controlled trial, the addition of baricitinib, an inhibitor of Janus kinases 1 and 2, to remdesivir was associated with shorter time to recovery (to hospital discharge or no longer requiring supplemental oxygen) and a greater likelihood of clinical improvement by day 15 [28]—as a result of this study, baricitinib became the first immunomodulator to receive emergency use authorization (EUA) for the treatment of COVID-19 by the US Food and Drug Administration (FDA). Finally, given the immunopathogenesis of severe COVID-19, there was early enthusiasm for selective IL-6 blockade with tocilizumab and/or sarilumab and its potential benefit for patients with severe COVID-19. However, multiple randomized trials and matched cohort studies have yielded mixed results [29–31], including in the SOT population [32]. Taken together, the data still suggest that there may be a role for these agents as adjunctive therapy in select patient populations with severe COVID-19—for example, preliminary results from the Randomized, Embedded, Multi-factorial, Adaptive Platform (REMAP-CAP) trial of tocilizumab and sarilumab suggest a significant reduction in mortality among patients treated with IL-6 antagonists compared to controls [33].

Immune Responses to Non-SARS-CoV-2 Coronaviruses in SOT Recipients

Human Coronaviruses

The burden of human coronavirus (HCoV) (e.g., HCoV OC43, HCoV 229E, HCoV NL63, and HCoV HKU1)

infection in the transplant population has been previously described [34], but few studies have explored details of the immune response to these common community-acquired respiratory viruses. Multiple studies have identified an association between symptomatic respiratory virus infection, including those due to HCoV, and subsequent development of chronic lung allograft dysfunction (CLAD) in lung transplant recipients [35–39]. In one of these studies, HCoV was the only viral agent found to be a time-dependent risk factor for CLAD development [39], but this association is likely not unique to coronaviruses. Hypothesized mechanisms for HCoV (and other respiratory virus) infection and later development of CLAD include T regulatory (Treg) cell dysregulation [40] or induction of exosomes containing lung-associated self-antigens [41]. Notably, pre-existing immunity to endemic HCoV (as measured by spike-protein-reactive T cells) has been found to be cross-reactive with SARS-CoV-2 [15, 42, 43] and may account for some of the heterogeneity in clinical outcomes seen in COVID-19.

Zoonotic Coronaviruses

Only two cases of SARS (due to the virus now named SARS-CoV-1) [44, 45] and three cases of Middle East respiratory syndrome (MERS, due to MERS-CoV) [46, 47] have been described in SOT recipients. While detailed immunologic assessments were not conducted in these patients, they did exhibit clinical features suggestive of an altered immune response, including atypical presenting features [46, 47], viremia [47], a high number of secondary cases consistent with increased or prolonged viral shedding [44], and a high case fatality rate (4 of 5 reported cases died).

Immune Responses to SARS-COV-2 in SOT Recipients

Initial clues that the immune response to SARS-CoV-2 may differ among SOT recipients came from observational cohort studies that described clinical manifestations and virologic outcomes that were different from the non-transplant population [48]. For example, in the largest published series of transplant recipients with COVID-19, investigators reported lower rates of fever, higher rates of gastrointestinal symptoms, more significant lymphopenia, and higher case fatality rates compared to those described in the general population [3–7, 49]. Other studies reported high rates of SARS-CoV-2 RNAemia [50] and prolonged shedding of viral RNA based on serial respiratory tract sampling [51•, 52–54]. Like in the non-transplant population, RNAemia has been associated with worse clinical outcomes in SOT recipients [51•]. Finally, although detection of subgenomic RNA in respiratory tract samples by nucleic acid amplification does not translate into the presence of infectious

virus, at least one study found an association between “immunocompromised” status (broadly defined by the investigators, but a category which included SOT recipients) and culture positivity in the respiratory tract [55].

In addition to clinical and virologic data, several isolated case reports and small (<5 patients) case series have also profiled the immune response to SARS-CoV-2 in SOT recipients. However, there are limited prospectively collected data directly comparing immune responses to SARS-CoV-2 in the transplant and non-transplant population. As a result, most conclusions about relative characteristics of inflammatory markers, cytokines, antibodies, and lymphocyte subsets in transplant recipients are based on comparisons made between studies, which may be challenging to interpret and generalize because of differences in the study populations (i.e., type of transplant, time since transplant, immunosuppressive regimen, severity of COVID-19 illness), sampling timepoints, and assay performance characteristics.

To provide the most comprehensive but meaningful synthesis of the published data, we focused our review on studies of transplant recipients that included five or more patients and which reported any data on immunologic endpoints. We included relevant findings from individual case studies or smaller cohorts when they provided additional nuance to the overall data (Table 1).

Innate Responses in Transplant Recipients

Most studies of transplant recipients with COVID-19 have only reported data on non-specific markers of inflammation (i.e., erythrocyte sedimentation rate, C-reactive protein, ferritin, D-dimer, lactate dehydrogenase, and procalcitonin) and IL-6 levels. No studies have conducted more detailed innate immune profiling among SOT recipients that might provide insight into subtle differences in the early inflammatory cascade in this patient population or evidence of a compartmentalized response as has been observed in non-transplant patients. Based on the limited available data, it seems early responses to SARS-CoV-2 infection are similar between SOT recipients and non-transplant patients. In studies that have compared SOT recipients with carefully matched non-transplant cohorts, levels of inflammatory markers and IL-6 are similar among hospitalized patients [8, 9, 10•, 62]. As in the non-transplant population, the levels of these inflammatory markers—specifically IL-6—correlated with disease severity in some studies [3, 56], but are imperfect predictors of disease progression. Whether select SOT recipients might benefit from combinations of proven or investigational immunomodulators is an area of ongoing research [63].

Humoral Responses in Transplant Recipients

The available data on humoral responses to SARS-CoV-2 in the transplant population come from case reports or small case

Table 1 Key studies of the immune response to SARS-CoV-2 infection in SOT recipients

Immune response	Reference	Study design	Relevant immune assays	Population	Key findings	Limitations
Innate	[56]	Observational cohort study	IL-6 measurement with a commercial chemiluminescent immunoassay	49 kidney transplant recipients in France with COVID-19 44 PCR-confirmed 2 diagnosed by serology 3 clinical diagnoses	CRP and IL-6 levels (as well as other markers of inflammation and coagulopathy) strongly predictive of severe COVID-19 and death Nasopharyngeal SARS-CoV-2 viral loads were not associated with disease severity 10.4% overall seropositivity rate	Only kidney transplant recipients No non-transplant patients for comparison No other cytokine measurements
Humoral	[57••]	Cross-sectional seroprevalence study	3 commercial SARS-CoV-2 antibody assays 1 anti-nucleocapsid antibody assay 2 anti-RBD assay	855 kidney transplant patients in the UK 69 tested positive 38 with PCR-confirmed SARS-CoV-2 infection (82% had received alemtuzumab induction) PCR-positive patients served as their own controls (pre-pandemic sera) 85 immunocompetent healthcare workers with PCR-confirmed SARS-CoV-2 infection were also tested using 2 of the same antibody assays	Widely differing performance characteristics of 3 antibody assays, including differences with the immunocompetent comparison group	Only kidney transplant recipients High rates of alemtuzumab induction therapy Only 1 of 3 assays detected IgM antibody No details of antibody titer data No assessment of neutralization
	[58]	Observational cohort study	Commercial anti-nucleocapsid antibody assay	10 SOT recipients (3 outpatients and 7 hospitalized) with PCR-confirmed COVID-19 in the USA	None 6 of 7 hospitalized patients had detectable antibodies 1 patient with severe illness (ARDS, shock) did not seroconvert Median time to seroconversion was 15 days	No non-transplant patients for comparison No details of antibody titer data No assessment of neutralization Limited follow-up and small sample size
	[51••]	Observational cohort study	Commercial anti-nucleocapsid and anti-spike antibody assay	40 kidney transplant recipients hospitalized with laboratory-confirmed COVID-19 in France 38 PCR-confirmed 2 diagnosed by serology	36 survivors seroconverted, whereas 4 non-survivors did not 13 had detectable IgM and/or IgG antibodies by day 14 All had seroconverted by days 15–28 Antibodies were maintained through day 59 No difference in antibody titers between severe and non-severe cases	Only kidney transplant recipients No non-transplant patients for comparison Authors did not report anti-nucleocapsid and anti-spike results separately No assessment of neutralization
	[59••]	Observational cohort study (follow-up to [51••])	Commercial anti-nucleocapsid and anti-spike antibody assay	29 kidney transplant recipients with laboratory-confirmed COVID-19 in France	21 of 29 (72%) had detectable IgG up to day 190	Only kidney transplant recipients No non-transplant patients for comparison Authors did not report anti-nucleocapsid and anti-spike results separately No assessment of neutralization
	[60••]	Observational cohort study	Commercial multiplex anti-nucleocapsid and anti-spike antibody assay	6 kidney transplant recipients hospitalized with COVID-19 5 PCR-confirmed 1 clinical diagnosis	All 7 patients with PCR-confirmed COVID-19 seroconverted by days 21–42 7 had anti-nucleocapsid IgG 5 had anti-spike IgG 3 had anti-spike IgM	Only kidney transplant recipients and small sample size Authors did not report titers from transplant and non-transplant patients separately No assessment of neutralization

Table 1 (continued)

Immune response	Reference	Study design	Relevant immune assays	Population	Key findings	Limitations
Cellular	[60••]	Observational cohort study	IFN-gamma ELISpot using overlapping 15mer SARS-CoV-2 peptide pools (representing structural and non-structural proteins)	5 kidney transplant recipients with suspected mild COVID-19 (outpatients that were PCR-negative) 2 hemodialysis patients with PCR-confirmed COVID-19 (1 hospitalized) 6 kidney transplant recipients hospitalized with COVID-19 5 PCR-confirmed clinical diagnosis 5 kidney transplant recipients with suspected mild COVID-19 (outpatients that were PCR-negative) 2 hemodialysis patients with PCR-confirmed COVID-19 (1 hospitalized)	In the 3 patients tested twice (2 transplant, 1 non-transplant), trend toward declining titers by day 60 All 7 patients with PCR-confirmed COVID-19 displayed CD4 ⁺ and CD8 ⁺ T cells reactive to at least 6 of 9 peptides (anti-spike reactivity was dominant) All 5 transplant patients underwent reduction of immunosuppression at time of diagnosis 3 PCR-negative patients had no SARS-CoV-2 reactive T cells	Only kidney transplant recipients and small sample size No assessment of T cell subsets and phenotype
	[61••]	Observational cohort study	Commercial anti-nucleocapsid antibody assay Flow cytometry for B and T cell assays and intracellular cytokine staining for T cell assays	18 kidney transplant recipients hospitalized with PCR-confirmed COVID-19 Banked PBMCs (pre-pandemic) from 36 kidney transplant recipients served as negative controls 14 COVID-negative and 16 COVID-positive non-transplant controls	16 transplant patients underwent antibody testing, and 60% had detectable antibodies (mostly between day 10 and 30) Transplant patients with COVID-9 had higher frequencies of B cell subsets (naïve, switched, activated) compared with uninfected controls No change in T _{FH} , plasmablast, or circulating plasma cell frequencies Reductions in effector and memory CD4 ⁺ and CD8 ⁺ T cells No evidence of exhausted T cells, unlike non-transplant patients with COVID-19 No differences in B or T cell populations by disease severity	Only kidney transplant recipients No assessment of neutralizing antibodies No assessment of memory B cells No assessment of SARS-CoV-2-specific T cell reactivity

series—which tend to be biased toward cases that failed to seroconvert [64, 65], had delayed seroconversion [66, 67], or had rapid loss of antibodies [68]—as well as seroprevalence surveys conducted at individual transplant centers [57•, 69–71], or observational cohort studies of transplant recipients with laboratory-confirmed COVID-19 [50, 51•, 58, 59•, 60•, 61•, 72].

Collectively, these data show that, similar to the non-transplant population, transplant recipients can mount SARS-CoV-2-specific antibodies within 1–2 weeks after the onset of COVID-19 symptoms and these antibodies may be durable for at least 2 months [51•, 58, 61•], and potentially up to 4 to 6 months [59•, 72] post-infection. Furthermore, a robust antibody response can be elicited regardless of illness severity [51•, 58, 61•] (two small studies of six and 18 patients, respectively, did report a higher [54, 72] and more durable [54] antibody response in patients who experienced severe illness), including in the first few weeks after transplantation and following asymptomatic infection.

Although these data provide reassurance regarding the potential for SOT recipients to mount a humoral immune response to SARS-CoV-2, they yield limited novel insight into unique aspects of the humoral response in this patient population, for several reasons: (1) Many studies only reported qualitative results (e.g., positive or negative) which precludes any comparison of the magnitude of the antibody response with non-transplant patients; (2) most studies measured antibodies at too few timepoints to derive meaningful conclusions about antibody kinetics, which may differ in transplant recipients; (3) studies utilized different antibody assays with variable targets and performance characteristics, making it difficult to definitively distinguish cases from controls or to evaluate qualitative differences in the antibody response (i.e., most studies measured anti-nucleocapsid rather than anti-receptor binding domain (spike) antibodies, and the former may not be neutralizing, and most studies measured antibodies using enzyme-linked immunosorbent assay (ELISA) rather than neutralization-based assays); (4) the number of patients with detectable antibodies was often too small to analyze for associations with clinically relevant baseline characteristics (such as organ type, time from transplant, or induction and maintenance immunosuppressive regimen); and (5) few studies directly compared transplant with non-transplant patients enrolled contemporaneously at the same site.

To date, only one study has directly compared humoral immune responses to SARS-CoV-2 between transplant and non-transplant recipients with and without COVID-19 [61•]. Using banked samples from uninfected kidney transplant recipients as negative controls, this study of 18 kidney transplant recipients with symptomatic COVID-19 found that most patients exhibited broad activation of B cell subsets (switched, activated, and memory) but not T follicular helper (T_{FH}) cells, as well as a robust anti-SARS-CoV-2

nucleocapsid IgM and IgG antibody response as measured by ELISA. The authors observed similar responses in non-transplant patients with COVID-19 admitted to the same center. The investigators could not identify any differences in the humoral response between transplant patients with mild, moderate, or severe COVID-19 illness (based on a 7-point ordinal scale), even though this has been observed in studies of non-transplant patients. Additionally, withdrawal of the anti-proliferative agent (e.g., mycophenolate) at the time of COVID-19 diagnosis did not seem to impact the magnitude of the antibody response—notably, the sample sizes in these analyses may have been too small to detect any differences. Finally, in three patients that underwent sampling at multiple timepoints, there was a trend toward lower percentages of B cell subsets (switched, activated, and memory) and antibody levels by 2 months after symptom onset.

Cellular Responses in Transplant Recipients

Although multiple studies have described profound lymphopenia among SOT recipients with COVID-19, we identified only two studies that conducted a more detailed evaluation of cellular immune responses to SARS-CoV-2 in this patient population. Candon et al. [60•] measured the frequency of SARS-CoV-2-reactive T cells using IFN-gamma enzyme-linked immune absorbent spot (ELISpot) among kidney transplant recipients with COVID-19—their cohort included five patients with PCR-confirmed infection (all of whom had moderate-severe disease and were hospitalized), six with suspected infection (but who were PCR-negative, and five of whom had mild disease and were managed in the ambulatory setting), as well as two non-transplant patients with end-stage renal disease on hemodialysis with PCR-confirmed moderate-severe COVID-19 that were used for comparison.

In this analysis, the kidney transplant patients with PCR-confirmed COVID-19 displayed broadly reactive SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells from 2 to 6 weeks after symptom onset, with frequencies similar to the non-transplant patients on hemodialysis (as well as those reported in the literature for non-transplant patients)—notably, all five of the transplant recipients underwent reduction of immunosuppression at the time of diagnosis of COVID-19 [60•]. Interestingly, of the six transplant patients who tested negative for SARS-CoV-2, none generated SARS-CoV-2-specific antibodies, and three had no detectable SARS-CoV-2-reactive T cells—five of these patients did not have their immunosuppression reduced at the time of diagnosis. These findings suggest not only that at least some of the suspected cases in this series did not, in fact, have COVID-19, but also that in the three PCR-negative patients who did have low levels of SARS-CoV-2-reactive T cells (but no antibodies), milder infection (and consequent continuation of immunosuppressive

therapy) may be associated with an attenuated immune response.

Hartzell et al. [61••] assessed both the frequency and phenotype of SARS-CoV-2-reactive T cells in 18 kidney transplant recipients with laboratory-confirmed COVID-19 and compared these with banked peripheral blood mononuclear cells (PBMCs) from uninfected transplant recipients as well as non-transplant patients with and without COVID-19 enrolled contemporaneously at the same center. Like non-transplant patients, the transplant patients with COVID-19 exhibited T lymphopenia, with a bias toward CD8⁺ T lymphopenia. There was no emergence of exhausted, anergic, or senescent T cell populations among the transplant patients, unlike what has been observed in some studies of non-transplant patients with severe COVID-19. The investigators could not identify any differences in CD4⁺ or CD8⁺ T cell responses between transplant patients with mild, moderate, or severe COVID-19 illness (based on a 7-point ordinal scale), though the sample size may have been inadequate to detect any association. This study was too small to provide insights on the durability of the T cell response or the induction of T cell memory in the transplant population, both of which are likely relevant to long-term protective immunity and the risk of reinfection or recrudescence infection.

Data Synthesis

Overall, as in the non-transplant population, in SOT recipients, SARS-CoV-2 infection triggers a broad array of pro- and anti-inflammatory cytokines, and the same innate immune responses that have been associated with severe disease in non-transplant patients have also been identified in transplant recipients. However, this is not a consistent observation and, in some studies, the degree of overlap of these markers among those with mild, moderate, and severe (and fatal) disease makes it difficult to draw any substantive conclusions about their individual prognostic value [73].

Similarly, based on very limited data, transplant recipients appear to be able to mount humoral and cellular responses of similar magnitude to non-transplant patients. However, larger and more detailed analyses will likely be needed to detect qualitative differences (for example, in kinetics or breadth of response) that may underlie the differences in clinical outcomes that have been observed among transplant recipients with COVID-19 in some studies. Ultimately, in the absence of a systematic (i.e., stratified by organ type, time since transplant, immunosuppressive regimen) and comprehensive (i.e., multiplex panels, immunophenotyping, systems biological approaches) assessment of immune responses in this patient population, we can draw limited meaningful conclusions about differences in the immune response to SARS-CoV-2 between SOT recipients and the general population.

Implications for SARS-CoV-2 Vaccines in Transplant Recipients

Vaccine Platforms and Transplantation

A number of vaccine platforms are being utilized to develop vaccines against SARS-CoV-2 [12•]. In the absence of a specific signature of the immune response to SARS-CoV-2 that is unique to transplant recipients, or an immunologic correlate of protection against COVID-19, it is difficult to devise a tailored vaccination strategy for SOT recipients [12•, 74]. Experience with licensed vaccines has shown that these patients mount less robust immune responses to vaccines compared with non-transplant patients regardless of vaccine type [75], though the specific impact of each component of transplant immunosuppression on vaccine immunogenicity is poorly understood. Nevertheless, these observations have implications for the anticipated immunogenicity and efficacy of the various SARS-CoV-2 vaccine platforms in this population (Table 2).

As of January 2021, two messenger RNA (mRNA) vaccines (mRNA-1273 and BNT162b2) have been given EUA by the US FDA. In phase III trials, these vaccines were more than 90% effective at preventing COVID-19, across all age groups and in pre-specified subgroups at high risk of severe disease [80, 81]. These trials specifically excluded patients receiving chronic immunosuppressive drug therapy (i.e., SOT recipients). Notably, prior to the COVID-19 vaccine studies, mRNA (and related DNA) vaccine technologies had been demonstrated to be immunogenic in non-transplanted individuals, but there were no pre-pandemic data on mRNA-based vaccines in SOT recipients, and only limited data on the closely related DNA vaccine platform in this patient population. A cytomegalovirus DNA vaccine was demonstrated to be immunogenic in allogeneic stem cell transplant recipients [82], but not kidney transplant recipients [77].

Multiple protein subunit vaccines against SARS-CoV-2 are also currently in clinical trials [12•]. Like the studies of mRNA vaccines, some, but not all of these trials are excluding patients receiving chronic immunosuppressive therapy. The principal advantages of these vaccines will be their simpler dosing schedules, storage requirements, scalability, and potential impact on disease transmission. In the absence of an adjuvant, subunit vaccines are known to be less immunogenic in SOT recipients [75], but many of the SARS-CoV-2 protein subunit vaccines currently under investigation are adjuvanted products.

Finally, several vectored vaccines using either human or chimpanzee adenovirus vectors have been demonstrated to be immunogenic and effective in non-transplant patients in phase III trials [83] and have been granted emergency use authorization in some countries. Similar to other live vaccines, live replicating vectored vaccines would likely not be recommended for use in SOT recipients and other

Table 2 Vaccine platforms used in SARS-CoV-2 vaccines (tested in phase III trials as of January 2021) and published data on immunogenicity and alloimmunity in SOT recipients

Vaccine platform	Example products against SARS-CoV-2	Evidence of immunogenicity of this vaccine platform in SOT recipients	Evidence on alloimmunity related to this vaccine platform in SOT recipients
mRNA	mRNA-1273 BNT162b2 CVnCoV	No data	No self-reported episodes of rejection in a national survey of 187 SOT recipients after a single dose of mRNA-1273 or BNT162b2 [76]
DNA	AG0302-COVID19 ZyCoV-D	ASP0113, a DNA-based cytomegalovirus vaccine (encoding glycoprotein B and phosphoprotein 65), was not immunogenic in kidney transplant recipients [77]	No difference in rates of rejection between ASP0113 and placebo [77]
Nanoparticle	NVX-CoV2373	No data	No data
Virus-like particle	CoVLP	Suboptimal immunogenicity of quadrivalent human papillomavirus (HPV) vaccine in SOT recipients [78]	No data
Protein subunit or peptide	ZF2001 EpiVacCorona SCB-2019	For most routine protein subunit or inactivated vaccines, SOT recipients generate less robust immune responses compared with non-transplant patients	No evidence of alloimmunity associated with routine vaccines Reviewed in [79]
Inactivated virus	BBIBP-CorV CoronaVac BBV152 A, B, C Inactivated WIV04 Inactivated KMS-1 QazCovid-in	Reviewed in [75]	
Adenovirus (Ad) vectored	Gam-Covid-Vac Ad26.COV2.S Ad5CoV	No data	No data
Chimpanzee Ad vectored	ChAdOx1/AZD1222	No data	No data

immunocompromised hosts, though high-quality safety data for live vaccines in these patient populations are limited [84].

SARS-CoV-2 Vaccine Safety and Alloimmunity

One theoretical concern about the use of SARS-CoV-2 vaccines in transplant recipients is the risk of inducing alloimmunity and potentially even allograft rejection. Based on large observational cohort studies of transplant patients with COVID-19, there has not yet been any signal linking natural SARS-CoV-2 infection with subsequent rejection, including in lung transplant recipients—whether there will be an association with late development of CLAD has yet to be seen. Vaccines could induce alloimmunity by triggering an immune response that is cross-reactive with the allograft, by stimulating previously alloreactive immune cells, or through the non-specific stimulatory effects of adjuvants that could lead to de novo alloimmunity. Indeed, three groups of investigators described de novo donor-specific antibody (DSA) detection among separate cohorts of kidney and heart transplant recipients that had received AS03-adjuvanted 2009 H1N1 pandemic influenza vaccines [85–87].

Importantly, the association between vaccines and alloimmunity and rejection is not a consistent observation

(Table 2). Despite their reactogenicity, in the trials of both mRNA-1273 and BNT162b2, there were no safety signals to suggest a heightened risk of autoimmune phenomena. In a national survey of 187 SOT recipients (64% of whom were front-line healthcare workers) who had received a single dose of either mRNA-1273 or BNT162b2, there were no self-reported episodes of rejection or autoimmune phenomena [76]. Similarly, in a systematic review of vaccine studies in SOT recipients, Mulley et al. [79] identified no increased risk of alloimmunity or allograft rejection following routine vaccines, though most of the studies included in this analysis focused on influenza vaccine. A systematic review of safety data specifically focused on AS03-adjuvanted H1N1 influenza vaccines in transplant recipients found no signal to suggest an increased risk of allograft rejection associated with receipt of this adjuvant [88]. In smaller studies of other investigational and licensed adjuvanted vaccines, no increased rates of alloimmunity or rejection have been reported, including an experimental monophosphoryl lipid A (MPL)-adjuvanted hepatitis B vaccine in kidney and liver transplant recipients [89–91], a licensed MF59-adjuvanted influenza vaccine (FluAd®) [92] and investigational CMV vaccine in kidney transplant recipients [93], or the recently licensed recombinant herpes zoster subunit vaccine (AS01B adjuvanted) in kidney transplant recipients [94].

Together, these data suggest that any concerns about the theoretical risk of alloimmunity related to SARS-CoV-2 vaccines must be carefully weighed against the very real risks of natural SARS-CoV-2 infection. The most recently published guidance from the American Society of Transplantation (AST) supports the use of SARS-CoV-2 vaccines in SOT recipients in regions where transmission continues at a high level [95].

Conclusions and Future Directions

Since the identification of SARS-CoV-2 at the beginning of 2020, much has been learned about the complex immunopathogenesis of COVID-19. Although SOT recipients and other hosts with altered immunity may exhibit an altered clinical phenotype compared with the general population (e.g., more atypical manifestations, more severe disease, increased viral shedding), the precise immunologic basis for these differences has yet to be characterized.

Given the ongoing nature of the pandemic, there continues to be an opportunity to more rigorously and systematically assess the immune response to SARS-CoV-2 in SOT recipients. This includes more detailed analyses of both the magnitude and quality of the immune response to both natural SARS-CoV-2 infection and vaccination, including kinetics, breadth, and durability, across a wider spectrum of organ recipients and immunosuppressive regimens. Such data could yield valuable insights that would guide appropriate management of immunosuppression, use of immunomodulatory agents, and vaccination strategies for SARS-CoV-2 as well as other typical and emerging pathogens in this vulnerable patient population.

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Declarations

Conflict of Interest Dr. Phadke was supported in part by Imagine, Innovate, and Impact (I3) Funds from the Emory University School of Medicine and through the Georgia CTSA NIH award (UL1-TR002378). Dr. Scanlon was supported by the NIH R38 Stimulating Access to Research in Residency (StARR) grant through the NIH/NIAID (5R38AI140299-02). Dr. Jordan reports receiving grants and non-financial support from CSL Behring during the preparation of this manuscript, and grants and personal fees from CSL Behring, Hansa Biopharma, Regeneron, and Amlyx outside the submitted work. Dr. Jordan has patents for the use of IL-6 inhibitors for desensitization and treatment of antibody-mediated rejection in transplant recipients, the use

of clazakizumab to desensitize and improve renal transplantation in HLA-sensitized patients and to treat chronic antibody-mediated rejection of organ transplants, and the use of calcineurin inhibitor-free CTLA4-Ig with anti-IL-6/IL-6R for long-term immunosuppression in solid organ transplant recipients, all licensed to CSL Behring. All are outside the submitted work. Dr. Rouphael was supported by the Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC) grant through the NIH/DAIT (5U19AI090023).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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