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Review

What Is New in Prophylaxis and Treatment of COVID-19 in Renal Transplant Patients? A Report from an ESOT Meeting on the Topic

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Abstract: I should highlight that this manuscript is not a formal review on the topic, but a report from an ESOT meeting held on 22 June 2022. The assumption of immunosuppressants exposes kidney transplant recipients to the risk of infections, including COVID-19 infection. A transplant patient having COVID-19 infection raises several questions, including whether the immunosuppressive therapy should be reduced with the consequent risk of favoring acute rejections. Patient vaccination before transplantation is probably the gold standard to avoid the risk of COVID-19 infection after transplantation. In the case of transplant patients, three measures may be undertaken: vaccination, use of monoclonal antibodies and use of therapeutic antiviral small molecules. Concerning vaccination, it is still debated which one is the best and how many doses should be administered, particularly considering the new variants of the virus. The onset of virus variants has stimulated researchers to find new active vaccines. In addition, not all transplant patients develop antibodies. An alternative prophylactic measure to be principally used for patients that do not develop antibodies after vaccination is the use of monoclonal antibodies. These drugs may be administered as prophylaxis or in the early stage of the disease. Finally, the small antiviral molecules may be used again as prophylaxis or treatment. Their major drawbacks are their interference with immunosuppressive drugs and the fact that some of them cannot be administered to patients with low eGFR.

Keywords: COVID-19 prophylaxis; COVID-19 treatment; kidney transplantation; vaccination; monoclonal antibodies; small antivirus molecules

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1. Introduction

Kidney transplant (KTx) recipients affected by COVID-19 infection present several challenges principally concerning prophylaxis and therapy.

SARS-CoV-2 has a great impact on immunocompromised individuals with multiple comorbid conditions, as is common in KTx recipients.

Severe disease in immunocompromised individuals may reflect the inability to mount an effective immune response, even after vaccination [1].

The assessment of which individuals will benefit from monoclonal antibodies and small molecular therapeutics is complicated by an incomplete understanding of the thresholds for a protective immunity.

Moreover, in transplant patients, a discordance exists between cellular and immune responses.

In addition, in the immunodominant spike (S) protein, 5016 different amino acid replacements or substitutions have been identified, and multiple deletions may be present. As variants emerged, natural antibodies, therapeutic monoclonal antibodies and some vaccine-elicited antibodies have become less effective in preventing disease progression [2].

Overall, initially, the mutation rates were thought to be rather low, but it was later well recognized that spike protein mutations by altered membrane fusion of virus and

host cells led to either altered pathogenicity and human-to-human spread, altered susceptibility to vaccine-induced immunity and an altered response to monoclonal and small-molecule therapeutics.

Additionally, multiple studies identified several variables associated with a poor humoral immune response, including older age, high-dose assumption of corticosteroids in the last 12 months, triple immunosuppression and the use of mycophenolate mofetil and belatacept.

On 16 June 2022, the European Society for Organ Transplantation held a meeting on the Prevention and Treatments of COVID-19 in Solid Organ Transplant Recipients.

This study is conducted to convey the main findings of the meeting, taking into account several papers on the topic and that were mentioned in the meeting. In addition, several guidelines, position statements or guidelines of international relevance have been considered [3–6].

In this study, we will examine new approved therapies with particular reference to:

(a) Vaccination;
(b) Monoclonal antibodies, examining pre-exposure prophylaxis with tixagevimab and cilgavimab (Eurisheld) and other monoclonal and polyclonal antibody products;
(c) Small antiviral proteins, such as Nirmatrelvir/ritonavir, Molnupivar and Remdesivir (RMD) with particular concern toward their interaction with immunosuppressive agents.

2. Vaccination

In normal conditions, after vaccination, the immune response includes neutralizing antibodies that inhibit the binding of the virus to the receptor and T cell responses that are detectable either after vaccination or natural infection. Antibodies have a main function in preventing infection; T cells and antibodies both contribute to the prevention of severe disease.

Two wide studies documented firstly the efficacy and safety of two mRNA SARS-CoV-2 vaccines in healthy subjects.

In one study, 43,548 participants underwent randomization to receive BNT162b2 or a placebo [7]. The conclusion of the study was that a two-dose regimen of BNT 162b2 conferred 95% protection against COVID-19. A different study evaluated the safety and efficacy of the mRNA-1273 vaccine. This vaccine is a lipid nanoparticle-encapsulated mRNA that encodes the full-length spike protein of the SARS-CoV-2 virus. The study was conducted in 99 centers in the United States involving 30,420 subjects assigned 1:1 to receive either the vaccine or a placebo [8]. The mRNA-1273 vaccine had an efficacy of 94.1% in preventing COVID-19.

Both studies were conducted in non-transplanted and healthy subjects and against the Delta variant of the virus.

In a different study, Hamm et al. [9] evaluated the decline in the antibody concentration 6 months after two doses of the SARS-CoV-2 BNT162b2 vaccine in 200 solid organ transplant (SOT) recipients and in 200 matched healthy controls. The decline of both cellular and humoral responses was higher in the transplant patients with respect to the healthy subjects, and risk factors for the decline were older age, treatment with mycophenolate and treatment with corticosteroids. The decline was higher in KTX recipients with respect to other SOT recipients.

Another study [10] conducted a systematic review and a meta-analysis to compare the seroconversion rate with two doses of BNT162b2 versus mRNA-1273 in SOT recipients. The conclusion of the study was that, in SOT recipients, a higher conversion rate was observed after vaccination with mRNA-1273 compared with BNT162b2 (Figure 1). The authors concluded that further studies are needed to verify whether this difference remains after a third dose of vaccination.

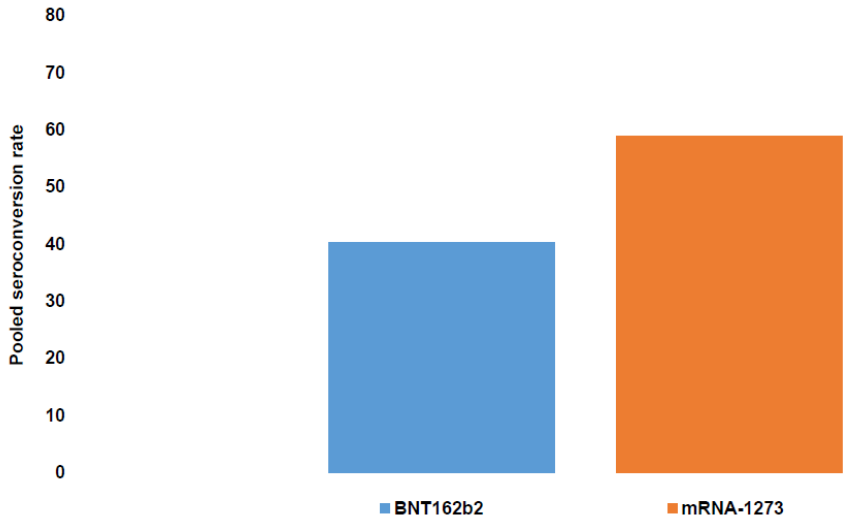

Figure 1. Relative seroconversion rate of BNT162b2 compared with mRNA-1273 = 79.5%.

A study by Liefeldt [11] examined the predictors of the serological response to SARS-CoV-2 vaccination in kidney transplant patients. The study found that predictors of a weak response were the age at vaccination, time after kidney transplantation, immunosuppression, estimated glomerular filtration rate (eGFR) at vaccination and lymphocyte count at vaccination (Table 1a). The time after transplantation had an important role in the immune response, because, in the early period, the higher immunosuppression and the higher incidence of rejection may prevent or reduce the immune response. The use of mycophenolate further impaired the response to vaccination and the authors hypothesized that erythrocyte IMPDH activity could be used to monitor mycophenolate treatment (Table 1b).

Table 1. (**a**) Multivariate analysis of factors associated with the serological response to vaccination after kidney transplantation according to the study of Liefeldt et al. [11]; (**b**) multivariate analysis of factors associated with the serological response to vaccination after kidney transplantation in MPA-treated patients after KTx transplantation.

Factors	Multivariate Analysis		
	OR	95% CI	*p* Value
	(**a**)		
Age at 2nd vaccination	0.98	0.96; 1.00	0.039
Time after kidney TX	1.06	1.02; 1.10	0.001
TAC + MPA + Steroid	0.15	0.08; 0.28	<0.001
CyA + MPA + Steroid	0.51	0.27; 0.96	0.038
TAC/CyA + Steroid	4.11	1.71; 9.90	0.002
eGFR at vaccination	1.03	1.02; 1.04	<0.001
Lymphocyte count at vaccination	1.12	1.06; 1.18	<0.001
CNI trough levels at vaccination	0.94	0.90; 1.00	0.036
	(**b**)		
Female	0.41	0.20; 0.83	0.013
Age at 2nd vaccination	0.96	0.94; 0.99	0.002
Time after kidney TX	1.07	1.01; 1.13	0.031
TAC MPA Steroids	0.43	0.20; 0.95	0.036
CyA MPA Steroids	1.30	0.57–2.98	0.534
eGFR at vaccination	1.03	1.01; 1.05	0.014
Lymphocyte count at vaccination	1.06	0.99; 1.14	0.077
CNI trough levels at vaccination	0.92	0.84; 1.00	0.040
MPA dose at vaccination	0.72	0.59; 0.87	0.001
IMPDH activity	0.34	0.25; 0.46	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; TAC, Tacrolimus; MPA, Mycophenolate acid; CyA, Cyclosporine; eGFR, estimated glomerular filtration rate; CNI, calcineurine; IMPDH, inosine monophosphate dehydrogenase.

The main message of Liefeldt's study is that, in addition to risk factors found by other authors, their study highlights the relevance of the MPA treatment.

Another study by Balsby et al. [12], in SOT patients, found that the antibody response after a third dose of BNT162b2 was improved, but the overall response was still low, with a significant ratio of non-responders. The predictors of a poor response were similar to those found in other studies. The KTx recipients were confirmed to be the lower responders (Figure 2).

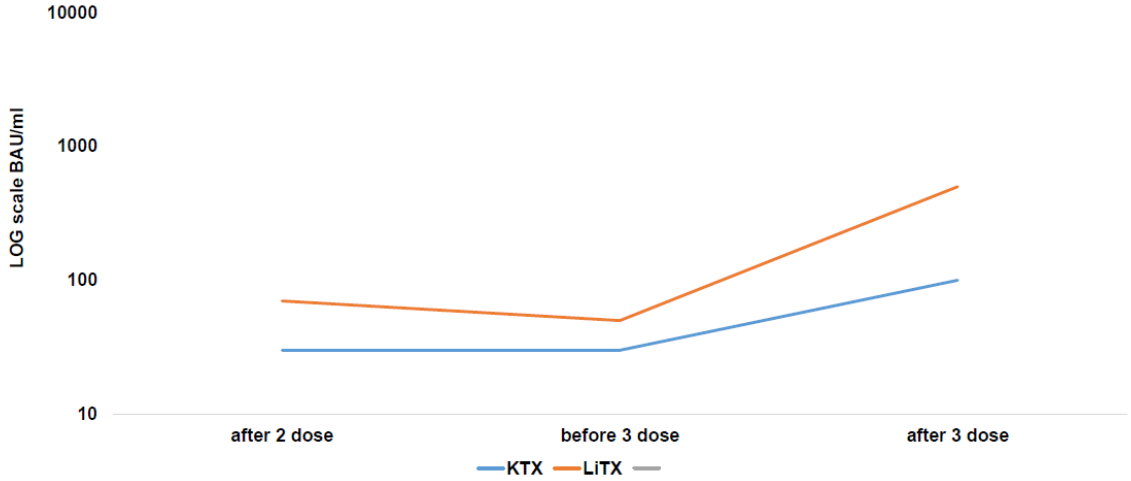

Figure 2. Anti-SARS-CoV-2 antibody titers according to the type of transplantation.

A study by Hod et al. [13] in 99 KTx patients documented the relevance of a third booster dose of BNT162b2. The study reported that a third dose increased both the level of neutralizing antibodies and receptor binding domain (RBD) antibodies in KTx patients. The results of both responders and non-responders are shown in Table 2.

Table 2. Univariate analysis of immune status before the third vaccine vs. post-third-vaccine in RTR according to the study of Hod et al. [13].

	Before 3rd Vaccine	Post-3rd-Vaccine	*p* Value
All cohort			
IgG-RBD GMT (95% CI)	0.79 (0.65–0.96)	3.08 (2.76–3.45)	<0.0001
NA GMT (95% CI)	17.46 (12.38–24.62)	362.2 (220.7–594.6)	<0.0001
Positive responders			
N (%)	32 (32.3)	85 (85.9)	<0.0001
=35IgG-RBD GMT (95% CI)	2.53 (2.07–3.11)	3.57 (3.28–3.88)	<0.0001
NA GMT (95% CI)	89.12 (53.03–149.8)	689.9 (456.3–1043)	<0.0001
Negative responders			
N (%)	67 (67.7)	14 (14.14)	<0.0001
IgG-RBD GMT (95% CI)	0.45 (0.39–052)	1.28 (0.87–1.86)	<0.0001
NA GMT (95% CI)	8.01 (5.92–10.84)	7.25 (2.42–21.71)	0.85

Abbreviations: CI, confidence interval; GMT, geometric mean titer; NA, neutralizing antibodies; RBD, receptor binding domain.

The study found that, after a third BNT162b2 booster dose, the humoral response assessed by both RBD IgG and neutralizing antibodies (NAs) significantly increased.

Protective values of RBD IgG and neutralizing antibodies, their interrelationship and factors influencing their levels.

In an initial study by Dimeglio et al. [14], 8758 healthy people were studied and followed over time. Approximately half of them received one or two doses of a vaccine. Regarding NAs, a titer of 64 to 128 afforded 94% protection and a titer of 256 provided full protection. Considering the RBD IgG, a concentration between 141 and 1700 binding antibody units (BAU/mL) provided 89.3% protection and full protection was provided by BAU/mL > 1700.

The study referred to healthy people and to wild-type or delta SARS-CoV-2.

In a further study, Dimeglio et al. [15] considered the protective values after the emergence of Omicron BA.1 and BA.2. They analyzed 259 healthy subjects after vaccination. A NA titer of 64 to 128 afforded 78.4% protection and 94% protection against the delta variant. Levels of BAU/mL as high as 20,000 provided only 87.7% protection.

A study by Suntronwong et al. [16] found a strong correlation between the binding and neutralizing antibodies after a third vaccination dose.

Almost all of the studies documented a decline over time in the antibody levels and, as expected, transplant patients had significantly lower levels, even after vaccination.

A recent systematic review and meta-analysis [17] documented again the immunogenicity and risk factors associated with a poor humoral immune response to any SARS-CoV-2 vaccines in SOT recipients. Overall, 112 studies were included in the meta-analysis with 11,713 SOT recipients. The antibody responses both for anti-spike antibodies and for neutralizing antibodies were higher according to the number of vaccines. The factors principally associated with a poor antibody response were older age, deceased donor, antimetabolite use, recent rituximab use and recent antithymocyte globulin exposure. The authors suggested that more effort is needed to modulate the risk factors associated with reduced humoral responses among recipients of SOT.

Several studies [18–20] documented the low immunization rate that occurs in several subjects receiving two doses of the mRNA-1273 SARS-CoV-2 vaccine. Among these were kidney transplant recipients, as highlighted by the study of Benotmane et al. [18] on 205 KT recipients that developed an immunization rate as low as 48%. Other non-transplant patients with a weak humoral immune response were older patients. The weak response occurred both after naïve COVID-19 infection and after BNT162b2 vaccination [19]. The study also suggested that, in these patients, vaccination after infection may be useful as it maintains a higher antibody titer for a long period.

Yang et al. [20] highlighted the relevance of the factor "age" in the response to vaccination in non-transplant patients. The authors studied the antibody response in 3648 adult patients, and their analysis found that a distinct antibody response characterized different age groups after two doses of the vaccine. The study suggested that age-targeted strategies for disease screening and management, as well as vaccine development, may be warranted.

A recent study by Mazzoni et al. [21] on non-transplant patients documented that SARS-CoV-2 infection and vaccination triggered long-living B cells and CD4 lymphocytes. Either in patients vaccinated after recovering from a COVID-19 infection and in patients vaccinated naïve, there was a significant decrease in all antibody levels, even if the decline was more pronounced in naïve individuals. The decline was detectable 8 months after vaccination or COVID-19 infection. Memory cells are still detectable after 8 months. The decrease in humoral immunity may account for reinfection. A third (booster) dose restores the humoral activity in vaccinated subjects, while the need of a booster dose is still an object of discussion for previously infected patients. The results of this study confirmed those of previous studies also performed in non-transplant patients, which documented similar data [22–25].

Interesting data were also documented by the already-cited study of Hamm [9]. Previous studies had already documented a reduced humoral response after two vaccine doses in SOT recipients [26–29]. The Hamm study evaluated the anti-receptor binding domain (RBD) immunoglobulins after two doses of BNT162b2 in SOT recipients versus controls and confirmed the reduced immunological response in SOT recipients. In addition, the response was weaker in KTx recipients than in those receiving other types of transplants.

In conclusion, in SOT recipients, two doses of vaccination confer to the patients low immunogenicity [30].

A randomized trial of a third dose of the mRNA-1273 vaccine in transplant recipients was conducted by Hall et al. [31]. The study documented an increase in anti-RBD antibodies, an increase in neutralizing antibodies and an increase in polyfunctional CD4 T cells after a third dose in SOT recipients.

The beneficial effect of three vaccine doses in SOT recipients was documented by the study of Kamar et al. [32], who highlighted a relevant increase in anti-SARS-CoV-2 antibodies after three doses of the mRNA vaccine BNT162b2 (Figure 3).

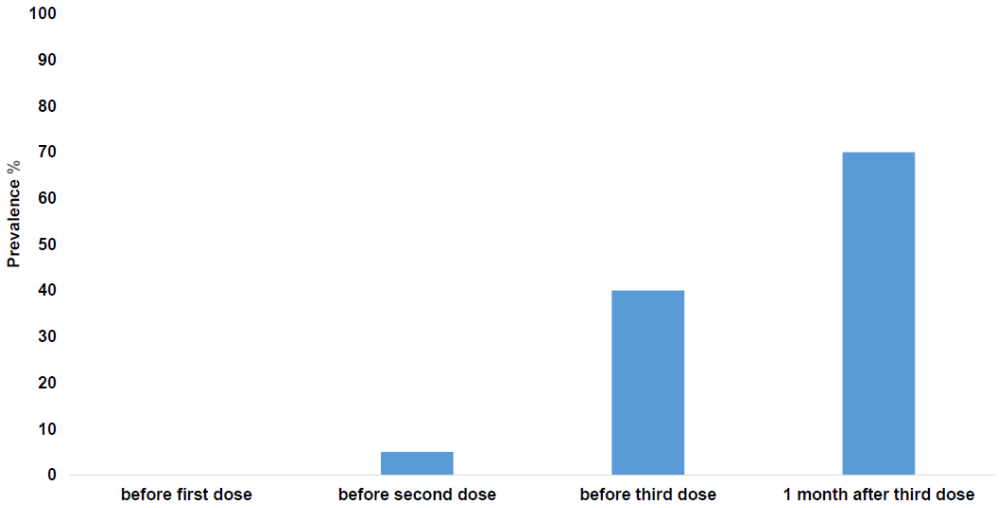

Figure 3. Prevalence of anti-SARS-CoV-2 antibodies after different doses of the mRNABNT162b2 vaccine.

In a different study, Kamar et al. [33] documented the efficacy of three vaccine doses (BNT162b2) in 850 SOT recipients. The study evaluated the anti-SARS-CoV-2 spike protein and neutralizing antibodies at 1 and 3 months after three doses. The study reported that only two-thirds of SOT recipients developed antibodies, while one-third remained unprotected. This study highlights the importance of immune monitoring to optimize vaccination in SOT recipients.

As 30% of SOT recipients do not develop protecting antibodies, several studies evaluated whether a fourth dose was effective in producing protective antibodies. The first study was conducted in France and documented an increase in the anti-SARS-CoV-2 antibody concentrations in SOT patients after four doses of the mRNABNT162b2 vaccine. Similarly, there was an increase in SARS-CoV-2-reactive IFN-gamma-producing cells [34].

A different study [35] documented, in 71 KTx patients, a relevant and protective increase after the fourth dose of an mRNA-1273 vaccine in a phase 4 study (NCT04801667).

However, in this study, as in another [36], patients with advanced age and with deceased donors may not have developed a protective immune response.

Other studies documented the beneficial effect of a fourth vaccine dose. In a case series of 92 KTx recipients [37], a significant increase in IgG antibodies against the spike protein was reported.

Benotmane et al. [38] documented, in 67 KTx recipients, that a fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improved serum neutralization against the Delta variant. In a different study, Masset et al. [39] highlighted the need for a fourth SARS-CoV-2 mRNA vaccine in strictly seronegative KTx recipients. After the fourth dose, 50% of patients developed protective antibody levels. Factors influencing the positive response were low steroid use, less lymphopenia and a longer time between the third and the fourth doses.

The identification of the Omicron variants changed the picture described due to the number of alterations in the spike glycoproteins that lead to antibody evasion and to a reduced immune response to vaccination.

The study of Iketani et al. [40], in non-transplant patients, documented that, after two or three doses, the levels of neutralizing antibodies were significantly lower in the case of omicron variants than against delta variants.

The study of Shen [41] collected other studies [42–45] and documented that, after two mRNA vaccine doses, there was minimal antibody-neutralizing level against omicron in non-transplant patients. Robust neutralization of omicron developed after a third mRNA vaccine dose. The magnitude of omicron neutralization after a third (booster) dose was

comparable to the delta neutralization after two doses. A fourth dose (second booster) had the potential to further improve the magnitude and durability of the immune response.

In Israel, Bar On et al. [46] selected 1,252,331 subjects aged 60 years and older. Half of the subjects received three vaccine doses and half received four doses. The rates of SARS-CoV-2 infection and severe COVID-19 were lower after a fourth dose of the BNT162b2 vaccine than after only three doses.

These data were confirmed by another similar study [47], even if this study highlighted higher protection in people older than 70 years.

Other studies [48] highlighted that the clinical characteristics of the subjects affected by the omicron variant were milder than those of subjects affected by previous variants. In any case, full vaccination is required for effective protection against the development of clinical severity.

In the case of transplant patients, several studies [49–51] reported a suboptimal antibody response against SARS-CoV-2 omicron variants with respect to the wild type (WT) and the delta variant after a third dose of an mRNA vaccine (Figure 4). In a different study [52], in transplant patients, a fourth dose of a COVID-19 vaccine did not induce neutralization of the omicron variant among SOT recipients with a suboptimal vaccine response.

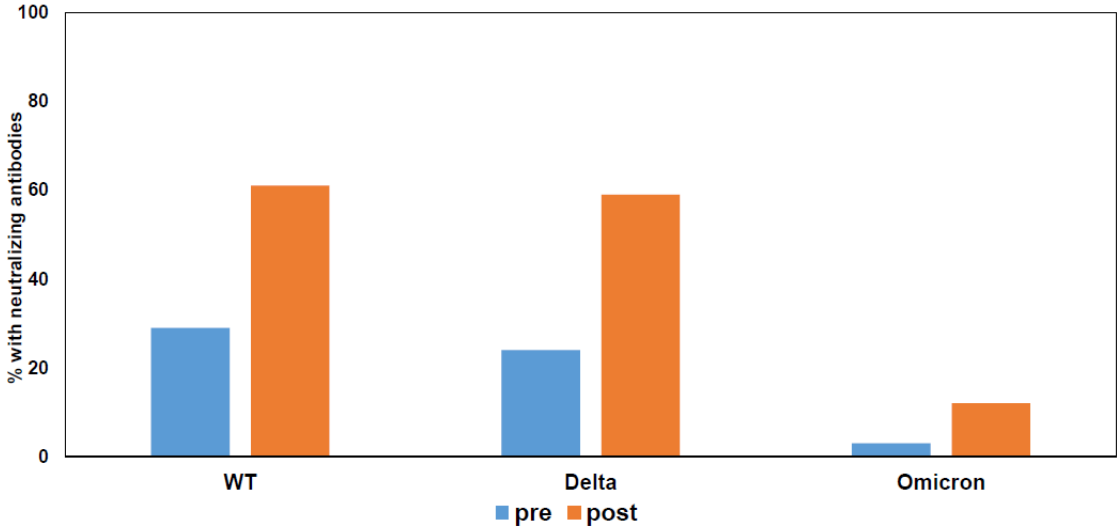

Figure 4. Proportion of KTx recipients with a positive neutralization response before and after the third vaccine dose.

An overall review of the effects of different doses of vaccine on the serological response is shown in Table 3. The review is the result of a study by Sakuraba et al. [53], who collected other epidemiological studies [54,55].

Table 3. Serological response after different vaccine doses in KTx recipients according to the studies of Sakuraba et al., Massa et al. and Masset et al. [50–52].

Kidney	Statistics				Transplant	Control
	A Serological response compared with controls after one dose of vaccine					
Kidney	Odds ratio	Lower limit	Upper limit	*p* Value		
	0.0063	0.0025	0.0160	<0.001	20/299	89/96
	B Serological response compared with controls after two doses of vaccine					
	0.0063	0.0025	0.0159	<0.001	208/655	271/273
	C Serological response compared with controls after three doses of vaccine					
	0.669	0.601	0.732	<0.001	132/197	

In conclusion, we may state that:

(a) The immune responses to COVID-19 mRNA vaccines include both B and T cells;

(b) The immune responses in SOT recipients are inferior to those obtained in both healthy controls and SOT candidates;
(c) Risk factors for non-responses include short duration from TX, treatment for acute rejection and use of Mycophenolate;
(d) Natural infection, and third and fourth doses improve the immune response;
(e) A third dose reduces the risk of severe COVID-19;
(f) A fourth dose may provide protection against the omicron variant;
(g) Vaccination of all SOT candidates and SOT recipients is a priority.

3. Monoclonal Antibodies

Monoclonal antibodies may be used either for COVID-19 prophylaxis or for the early treatment of COVID-19 infection. We have already described that, despite receiving three or four doses of a vaccine, not all patients are protected, particularly patients with reduced immunocompetence, such as transplant patients.

There are two strategies to protect patients with a weak immune response to a third dose or with no response at all.

We may proceed with an additional vaccine dose or with the aid of pre-exposition monoclonal antibodies.

REGEN-COV is a combination of two neutralizing monoclonal antibodies, casirivimab and imdevimab, that bind to the receptor-binding domain of the spike protein [56,57].

A trial with the use of REGEN-COV administered subcutaneously was conducted in 112 sites [58]. A total of 1505 participants neither having received a transplant nor being on a waiting list for transplantation and without any evidence of previous or ongoing infection were assigned to receive REGEN-COV or a placebo. At the follow-up, 7.8% of participants in the placebo group developed symptomatic infection versus 1.5% in the REGEN-COV group, with a significant difference ($p < 0.001$). This study documented the efficacy and safety of REGEN-COV. Almost simultaneously, another study [59] highlighted the efficacy of a different combination of monoclonal antibodies (bamlanivimab–etesevimab), as documented by the study of Dougan et al. [60]. All these studies were conducted in healthy, non-immunocompromised subjects.

After a recommendation of the France Authorities for Health [61], Dimeglio et al. [62] afforded the possibility to SOT recipients who were not responders or weak responders to receive casirivimab and indevimab in two distinct doses. Out of 478 patients, 182 received treatment while 296 remained untreated for different reasons. In the follow-up period of 60 days, no SARS-CoV-2 infection was verified in the treated group versus 4.4% infection in the non-treated group. In a different study, Ducloux et al. [63] obtained similar results with a combination of monoclonal antibodies in KTx recipients. Out of 119 KTx recipients who did not develop protective antibodies after vaccination, 88 were treated versus 31 not treated. No COVID-19 infection developed in monoclonal treated patients, while 16% of infections occurred in non-treated patients. The authors conclude that treatment with monoclonal antibodies conferred protection in immunocompromised patients.

This state-of-the-art changed with the advent of the Omicron variants.

Kamar et al. [64] reported an Omicron breakthrough infection in a KTx patient administered pre-exposition casirivimab and imdevimab monoclonal antibodies. The infection occurred despite a high concentration of anti-S antibodies that usually conferred 100% protection against non-Omicron variants. This highlights that very high anti-S antibodies are required to prevent Omicron infection. In the study of Planas et al. [65], the authors examined Omicron's sensitivity to nine monoclonal antibodies that have been clinically approved or studied in trials [66]. The authors found that Omicron was completely or partially resistant to all monoclonal antibodies tested. Previous studies have already documented the reduced sensitivity of Omicron to monoclonal antibodies [67,68]. The study of Planas [65] documented a considerable escape of SARS-CoV-2 Omicron from antibody neutralization. All these studies were conducted in non-transplant patients.

A different approach involves the use of a different monoclonal antibody combination (AZD7442) composed of tixagevimab and cilgavimab. Tixagevimab and cilgavimab bind to distinct epitopes of the SARS-CoV-2 spike protein receptor binding site, neutralizing the virus [69–71]. In an ongoing phase 3 trial involving 5197 participants randomized to receive either AZD7442 or a placebo, the safety and efficacy of AZD7442 was documented in healthy subjects [72] (PROVENT trial, NCT04625725). The study was conducted in non-transplant patients, but at risk of SARS-CoV-2 infection.

The association of tixagevimab and cilgavimab has been named Evushled. A study by Bertrand et al. [73] in KTx recipients compared Evusheld-treated patients with vaccinated and protected patients and with patients receiving the association of casirivimab and imdevimab. Patients treated with Evusheld had similar outcomes to vaccinated patients, while patients treated with casirivimab–imdevimab exhibited higher infection rates, principally due to the Omicron variants.

However, another relevant study on prophylaxis induced by Evusheld in KTx recipients [74] documented that less than 10% of patients treated with Evusheld were able to neutralize the Omicron BA.1 variant when administered a dose of 300 mg. Therefore, the Food and Drug Administration (FDA) recommended the revision of Evusheld dosing [75]. Overall, the Omicron variant represents a problem in the use of monoclonal antibodies as a prophylactic measure. Indeed, in the study of Iketani [40], BA.2 exhibited marked resistance to 17 of the neutralizing monoclonal antibodies tested.

The question of whether an increased dosage of Evusheld could achieve adequate protection without collateral effects remains open.

A different way to use monoclonal antibodies against SARS-CoV-2 is to administer the antibodies not as a prophylaxis, but as an early treatment in patients already affected by COVID-19 infection. A study by Mazzotta et al. [76], in line with other previous studies [77,78], compared the effectiveness of casirivimab/imdevimab with that of bamlanivimab/etesevimab as an early treatment in non-hospitalized and non-transplant patients with COVID-19. Worsening of the infection occurred in 6.3% of patients treated with bamlanivimab/etesevimab versus 2% of patients treated with casirivimab/imdevimab, with a significant difference. The main limitations of the study were that it was conducted in non-immunocompromised patients and in patients not affected by the Omicron variant. Similar limitations were present in a study that aimed to evaluate the early treatment of COVID-19 with the SARS-CoV-2-neutralizing antibody sotrovimab [79]. Sotrovimab, also known as VIR-7831, is an engineered human monoclonal antibody acting against SARS-CoV-2 and other sarbecoviruses [80]. In a phase 3 study, 583 patients were enrolled from 37 sites and admitted to receive sotrovimab or a placebo. All patients had symptomatic COVID-19 infection and were not affected by the Omicron variant. The effectiveness of sotrovimab was documented by a study that demonstrated no progression of the disease in the treated group.

In a different study [81], 51 patients with a large prevalence of immunocompromised or transplanted subjects were successfully treated with sotrovimab. The median SARS-CoV-2 nucleoprotein (NP) viral load decreased from 7.1 log10 copies/mL before sotrovimab infusion to 5.1 log10 copies/mL 7 days post-infusion. No sotrovimab-resistant spike mutations were detected before infusion, but 53% of these patients had acquired sotrovimab-resistant mutations 7 to 21 days post-treatment. Previously, in vitro studies had shown that sotrovimab could trigger a resistant spike protein due to mutations at positions 340 and 337 [82]. All these data call for a close monitoring of patients treated with monoclonal antibodies for the possibility of the emergence of mutations and resistance to treatment.

A relevant study on the efficacy of monoclonal antibodies in KTx recipients was conducted in France [83]. The antibodies (either bamlanivimab alone, bamlanivimab/etesevimab or casirivimab + imdevimab) were administered to 80 KTx recipients affected by COVID-19 infection and compared with 155 controls. COVID-19-related hospitalization, 30-day admission to an intensive care unit (ICU) and death within 30 days were the endpoints. The early administration of monoclonal antibodies was beneficial, and the overall effects are

presented in Table 4. These data demonstrate the efficacy of monoclonal antibodies administered to KTx recipients with a mild COVID-19 form and highlight that monoclonal antibody administration for SOT recipients with a weak vaccine response should be considered. In addition, the study confirmed the results of previous studies conducted on transplant patients [84–87] who used different associations of monoclonal antibodies.

Table 4. Outcomes at 1 month of kidney transplant recipients treated or not with anti-SARS-CoV-2 monoclonal antibodies [80].

Outcomes	MoAb Group	Control Group	*p* Value
Severe COVID-19, *n* (%)	3 (3.8)	30 (19.4)	0.001
Admission to ICU, *n* (%)	2 (2.5)	24 (15.5)	0.002
Need for mechanical ventilation, *n* (%)	0 (0.0)	18 (11.6)	<0.001
Death, *n* (%)	1 (1.25)	18 (11.6)	0.005

Abbreviation: ICU, intensive care unit.

Another study evaluated the association of monoclonal antibodies with remdesivir (RMD) as an early treatment in immune-compromised patients with unsatisfactory responses to vaccination [88]. The study was conducted either in transplant or non-transplanted patients. The conclusions of the study were that the association of RMD and mAbs did not cause relevant adverse effects while resulting in good outcomes for the disease.

A more recent study on the effectiveness of early administration of sotrovimab was conducted on 498 high-risk, non-immunocompromised and immunocompromised patients affected by the B.1.1.529 Omicron variant [89,90]. The study documented the efficacy of sotrovimab in preventing hospitalization and mortality in both immunocompromised and non-immunocompromised COVID-19 patients affected by the Omicron variant.

In an interesting study, sotrovimab administration in vaccinated and not vaccinated KTx recipients with SARS-CoV-2 infection due to the Delta and the Omicron BA.1 surges were evaluated [91]. Surprisingly, the outcomes were similar, despite Omicron's mildness [92]. This fact could be ascribed either to Omicron's immune evasion or to the inadequate immune response of KTx recipients.

Again for sotrovimab, the time of its administration after the onset of COVID-19 symptoms is critical. In a study on KTx recipients, Villanego et al. [93] compared 46 patients who received sotrovimab <5 days after the onset of symptoms with 36 patients who were treated >5 days. The results of the COVID-19 outcomes were critical, and are shown in Table 5.

Table 5. Outcome comparison between kidney transplant recipients treated with sotrovimab early in the onset of symptoms and those treated late [90].

Variable	<5 Days (*n* = 46)	5 Days (*n* = 36)	*p*-Value
Ventilator support, *n* (%)	1 (2.2)	13 (36.1)	<0.001
ICU admission, *n* (%)	1 (2.2)	9 (25)	0.002
Death, *n* (%)	1 (2.2)	6 (16.7)	0.02

In conclusion, according to the data available, early exposition to monoclonal antibodies indicates that the association of casirivimab and imdesimab is effective for treating the Delta variant. Sotrovimab had no efficacy against the Omicron variants BA.1 and BA.2. The association of tixagevimab and cilgavimab is under evaluation for the treatment of the Omicron variant BA.2.

The main characteristics of the monoclonal antibodies are shown in Table 6.

Table 6. Characteristics of monoclonal antibodies for the treatment of COVID-19. 2022.

Class and Agent	Dosing	Place in Therapy	Drug-Drug Interactions	Adverse Effects	Special Consideration for TX Recipients
Monoclonal antibodies	Bemlanivimab 700 mg plus etesevimab 1400 mg IV as a single dose Casirivimab 600 mg plus imdevimab 600 mg IV/SQ as a single dose Sotrovimab 500 mg IV as a single dose	NIH Guidelines # Casirivimab plus imdevimab or sotrovimab recommended for outpatients with mild to moderate COVID-19 # Recommend against use of bamlanivimab plus etesevimab # Recommend against use in hospitalized patients outside a clinical trial WHO Guidelines # Class not addressed IDSA Guidelines # Recommended for ambulatory patients with mild to moderate COVID-19 at high risk	May decrease the effects of COVID-19 vaccination; postpone administration of COVID-19 vaccine until at least 90 days after treatment	Hypersensitivity Pruritis Injection site reactions Fever	# Authorized under FDA EUA # Administer in healthcare settings # Monitor patient for at least 1 h post-administration # Use of bamlanivimab alone and bamlanivimab plus etesevimab is not recommended due to decreased susceptibility of SARS-CoV-2 variants

4. Direct-Acting Small-Molecule SARS-CoV-2 Antivirals

These compounds do not target the variable spike protein, but target either the viral RNA-dependent RNA polymerase (RdRp) or the viral main protease (Mpro) [94]. Our study will consider three products: Remdesivir, which was the first antiviral approved to treat COVID-19; Molnupivar, an inhibitor of the viral RdRp [95]; and Nirmatrelvir, which is an irreversible inhibitor of SARS-CoV-2 Mpro. This compound, when co-formulated with ritonavir, has been named Paxlovid [96]. In vitro and preliminary in vivo studies [86] documented that these compounds maintained their activity against all SARS-CoV-2 variants of concern (VOCs), Omicron included.

These findings were confirmed by other studies [97], confirming the effectiveness of antiviral therapies against highly transmittable variants of SARS-CoV-2.

The same antiviral treatments for COVID-19 are recommended by an update on the treatment for COVID-19 recently published by the British Medical Journal [98].

A wide, recent study [99] confirmed, based on 40,776 non-transplant patients affected by COVID-19, the effectiveness of early molnupivar or nirmatrelvir–ritonavir treatment in hospitalized patients affected by the Omicron variant BA.2. Though this was a retrospective study, according to the authors, it was the first study to document, from a large number of patients, the efficacy of the antivirals when administered within 2 days of admission to the hospital. An overview of these antiviral molecules is shown in Table 7.

The use of the antivirals in SOT patients and, in particular, in KTx recipients faces two major problems: the efficacy and safety in immunocompromised patients and the interactions with immunosuppressants.

Table 7. Overview of SARS-CoV-2 antivirals.

	Nirmatrelvir/Ritonavir (Paxlovid)	**Molnupiravir (Lagevrio)**	**Remdesivir (Veklury)**
Population	Age > 12 years and >40 kg. Mild to moderate COVID-19 and high risk of progression to hospitalization or death. EMA and FDA approved	Age > 18 years. Mild to moderate COVID-19 and high risk of progression or death. EMA and FDA approved	Age > 12 years and >40 kg requiring supplemental oxygen. EMA and FDA approved (in and out of hospital)
Efficacy (high-risk population)	NNT (number needed to treat) = 18 (all cause hospitalization or death)	NNT = 35 (all cause hospitalization or death) when administered within the first 5 days of symptom onset	NNT = 22 (all cause hospitalization or death)
Drug interactions	Serious concern (ritonavir strongly inhibits CYP3A4)	Negligible	Monitor when co-administered with strong CYP3A4 inducers/inhibitors
Common side-effects	Dysgeusia and diarrhea	Diarrhea, nausea, anemia and potentially mutagenicity	Bradycardia, drug-induced liver injury and acute kidney injury
Renal/hepatic impairment	Dose adjustment with moderate renal impairment	No dose adjustment required	Not recommended if eGFR < 30 mL/min
Pregnancy	Contraindicated	Contraindicated	Reassuring data
Activity vs. variants	All known variants	All known variants	All known variants

A study [100] evaluated the early outcomes and renal functioning following antiviral treatments after KTx in patients affected by COVID-19. Ten of them received generic antivirals and eight received RDV. A proportion of 24% of the patients had acute kidney injury (AKI) at admission. Upon discharge, more patients treated with RDV exhibited a decrease in the eGFR, but the majority of patients returned to the baseline eGFR within one month after discharge. Due to the beneficial effects of antivirals, the authors concluded that these drugs appeared to be safe, without affecting renal function. A different study from Northern Italy [101] evaluated the effect of early RDV administration to prevent severe COVID-19 in SOT recipients. Seven out of twenty-four patients received pre-emptive RDV with a 3-day course. There was a significant reduction in the hospitalization rate in outpatient SOT recipients in contrast to the clinical worsening of the already-hospitalized SOT recipients. The authors highlighted the efficacy of RDV when administered as a pre-emptive drug before hospitalization. In a different retrospective cohort study [102], 38 hospitalized KTx recipients received 5-day RDV treatment versus 127 who received a standard-of-care treatment. Mortality was significantly reduced (39% vs. 83%) and the eGFR values improved at discharge.

In a different study [103], Radcliffe et al. evaluated the outpatient COVID-19 therapies in SOT recipients during the Omicron surge.

In this study, 122 patients with SOT and with COVID-19 diagnosed as outpatients were evaluated. Forty-nine patients received molnupivar and were compared with twenty-four patients who received the monoclonal antibody sotrovimab as outpatients and with forty-eight patients who received the standard-of-care therapy. The results of the study indicated that outpatient therapies are important in the management of mild to moderate COVID-19 in SOT recipients. According to the study, patients receiving molnupivar and sotrovimab had a reduced hospitalization rate and death, also when affected by the Omicron surge.

A similar study evaluated nirmatrelvir/ritonavir, sotrovimab and no SARS-CoV-2-specific treatment [104]. The results were, overall, the same and support the use of SARS-CoV-2-specific agents in the treatment of SOT recipients with COVID-19 infection.

Among the antiviral agents, Remdesivir and Nilmatrelvir/Ritonavir (Paxlovid) seem to be the most effective, but a major problem of RMD is the need for intravenous administration. A major problem with the use of Paxlovid is a severe drug–drug interaction due to the CYP3A inhibition by ritonavir, which can strongly increase the blood concentrations of

calcineurin inhibitors (CNIs) [105]. Several studies documented the dangerous interaction between Paxlovid and CNIs. A study by Salerno et al. [106] documented the risk of reaching supratherapeutic TAC concentrations after restarting the intake of the drugs. According to the authors, physicians should carefully re-introduce CNIs after the completion of a Paxlovid course. Prikis et al. [107] reported a case study on Paxlovid and TAC interaction in a KTx recipient. Wang et al. [108] also reported a dangerous interaction between Paxlovid and TAC in four SARS-CoV-2-infected KTx recipients. A recommendation on how to manage the interactions was published by Lange et al. [109]. The study suggested interrupting CNIs or mammalian target of rapamycin (mTOR) inhibitors during the Paxlovid course and to start taking the immunosuppressants again 2–3 days after the end of the Paxlovid course. Monitoring the drug levels was also highly recommended. Other recommendations are to not use RMD or Paxlovid with an eGFR of less than 30 mL/min.

Paxlovid interacts with several immunosuppressants. A useful guideline on how to manage these drugs was described by the Guidelines of the French Society of Pharmacology and Therapeutics [110], as shown in Table 8.

Table 8. Guidelines of the French Society of Pharmacology and Therapeutics (SFPT).

Immunosuppressive Drug	Nature and Magnitude of the Effect	Therapeutic Strategy
Tacrolimus	Increase in tacrolimus exposure by 40-fold	Administer 1/8 of the usual daily dose (DD) on day 1, then stop. Administer 1/2 of the DD on day 6, then 3/4 on day 7 and restart usual DD on day 8. Alternative for low immunological risk: start nirmatrelvir/ritonavir 12 h after the last intake of tacrolimus and restart tacrolimus at usual DD 24 h after the last antiviral dose. TDM if possible
Cyclosporine	Increase in cyclosporine exposure by 8-fold	Administer 1/5 of the usual DD every day of nirmatrelvir/ritonavir treatment. Administer 1/2 of the DD on day 6, then 3/4 on day 7 and restart usual DD on day 8. TDM if possible
Everolimus/Sirolimus	Increase in everolimus and sirolimus exposure by 15- and 11-fold, respectively	Administer 1/8 of the usual DD on day 1, day 3 and day 5. Usual DD can be restarted on day-7. TDM if possible
Mycophenolate mofetil	Weak interaction expected. Possible decrease in mycophenolic acid exposure	The dosage can be maintained

Abbreviation: TDM, therapeutic dose monitoring.

5. Conclusions

The best prophylactic measure is to administer all transplant candidates the full cycle of the SARS-CoV-2 vaccine before transplantation.

A two-dose vaccination is not adequate to protect all SOT recipients, and a third or a fourth dose is recommended [53–55].

To evaluate the level of protection against severe COVID-19, the titer of anti-spike IgG may be useful. The absence of any detectable antibody indicates the lack of effective protection and indicates that SOT recipients need additional protection. Such patients need an additional booster vaccine dose, possibly against the dominant virus variant circulating [33,34].

The administration of the vaccine should be avoided within the first 3 months after transplantation or in patients recently treated with lymphocyte-depleting therapies [11]. In such cases, is better to postpone the vaccination.

Immunosuppressive drugs limit the immune response after vaccination, but the reduction of the immunosuppressant may cause rejection. However, in SOT recipients with the absence of antibodies in response to vaccination, over one year from transplantation and with stable graft function, a reduction of the immunosuppressive drugs may be

evaluated under strict medical control, as recommended by several guidelines and position statements, including the ESOT recommendation [3].

Patients without an antibody response after 3–4 doses should be treated with prophylaxis with monoclonal antibodies [61,62]. The risk of potential resistance of new variants against the administered antibodies should be considered [74,75].

Antiviral molecules may be administered to patients with COVID-19 infection with concern regarding drug–drug interference with immunosuppressive drugs [105,107].

RMD should not be administered to patients with eGFR less than 30/mL/min [109].

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