

## Approach to infection in immunosuppressed patients

Francisco Javier Candel<sup>1,2,6,7,8</sup>  
Cándido Pardo Rey<sup>2,4,6,7</sup>  
Juan Ignacio Torres-González<sup>2,7</sup>  
Paula Fernández-Vega<sup>2,7</sup>  
Marcos Fragiél<sup>2,3,6,7</sup>  
David Oteo<sup>2,3,7</sup>  
Enrique del Toro<sup>2,3,7</sup>  
Mónica Vega-Bayol<sup>2,3,7</sup>  
Cristina Outon<sup>2,3,7</sup>  
Marta Encabo<sup>2,3,7</sup>  
Agustín García-Marugán<sup>2,7</sup>  
Sara Resino<sup>2,7</sup>  
Dolores Parra<sup>2,7</sup>  
Mayra Matesanz<sup>5,7</sup>  
Francisco J. del Rio Gallegos<sup>2,4,6,7,8</sup>

### COVID-19 in donation and transplant

<sup>1</sup>Clinical Microbiology and Infectious Diseases.  
<sup>2</sup>Transplant Coordination and Cell Tissue Bank.  
<sup>3</sup>Emergency Department.  
<sup>4</sup>Intensive Care Unit.  
<sup>5</sup>Internal Medicine Division.  
<sup>6</sup>IdISSC Health Research Institute.  
<sup>7</sup>Hospital Clínico San Carlos.  
<sup>8</sup>Department of Medicine. School of Medicine. Complutense University. Madrid. Spain.

Revista Española de Quimioterapia  
doi:10.37201/req/s03.13.2022

#### ABSTRACT

SARS-CoV-2 infection has had a major impact on donation and transplantation. Since the cessation of activity two years ago, the international medical community has rapidly generated evidence capable of sustaining and increasing this necessary activity. This paper analyses the epidemiology and burden of COVID-19 in donation and transplantation, the pathogenesis of the infection and its relationship with graft-mediated transmission, the impact of vaccination on donation and transplantation, the evolution of donation in Spain throughout the pandemic, some lessons learned in SARS-CoV-2 infected donor recipients with positive PCR and the applicability of the main therapeutic tools recently approved for treatment among transplant recipients.

**Keywords:** COVID, donation, transplantation, epidemiology, transmission, immunity, therapy

#### EPIDEMIOLOGY AND BURDEN OF COVID-19 IN DONATION AND TRANSPLANT

As in the rest of the population and according to multicenter studies, the main risk factors for acquisition and poor outcome after COVID-19 are age over 65 years (OR 6.01) and comorbid conditions, such as cardiovascular disease (OR 4.58) or its risk factors (hypertension (OR 2.95), diabetes (OR 3.07), overweight or smoking (OR 2.04)), chronic obstructive pulmonary disease (COPD) (OR 6.66) or chronic renal failure (OR 5.32) [1-7].

A retrospective North American study of 482 solid organ transplant (SOT) recipients during the first wave (March-May 2020, 50 centers, 66% kidney, 15% liver, 11.8% heart and 6% lung recipients), revealed a need for hospital admission of 78%, mechanical ventilation of 27% and mortality of 18% [8]. In this study, the risk factors mentioned above stood out significantly. When specifically analyzing the transplantation process, the worst clinical outcome correlated with lung transplantation and with some immunosuppressive regimens (especially steroids and anticalcineurin drugs). The COVID-19-infected renal recipients were older than 60 years, 5 or more years after transplantation, treated with steroids, tacrolimus, and mycophenolate. Most patients developed pneumonia (81%) and more than 30% had gastrointestinal symptoms. Comorbidities, the elderly, those with grafts younger than 1 year and those with graft dysfunction failed worse outcomes. The infected liver recipients were also older than 60 years. The main risk factor for mortality was liver cirrhosis in patients with Child C or MELD  $\geq$  15, dyspnea and comorbidities (50%-60%), also immunosuppression with mycophenolate or tacrolimus-free regimens. One third developed gastrointestinal symptoms and one third developed severe COVID-19 (need for ICU admission, mechanical ventilation, or death). Overall mortality was 20-22%. Lung recipients with COVID-19 developed acute respiratory distress syndrome in more than half of the cases (58%) and mortality was 46%, twice as high as in other solid organ transplants. An Indian cohort with 250 patients [9] and the Spanish series with 778 solid organ and hematological recipients from February to July 2020 [10] showed similar results (hospital admission 89%, mechanical ventilation 10%, adult respiratory distress syndrome 36% and mortality 27%).

However, after correction for risk factors associated with mortality in multivariate analysis, only age over 60 years and lung transplantation were significantly correlated with prognosis [10]. A French study of 306 kidney transplant recipients and 795 non-transplant controls again demonstrated no difference in 30-day mortality, when adjusted for age and co-

Correspondence:  
Francisco J Candel, MD, PhD  
Clinical Microbiology and Infectious Diseases.  
Transplant Coordination and Cell Tissue Bank.  
IdISSC Health Research Institute.  
Hospital Clínico San Carlos.  
Associate Professor. School of Medicine.  
Complutense University. Madrid. Spain.  
E-mail: franciscojavier.candel@salud.madrid.org

morbidity [11]. A Spanish comparative study between kidney transplant recipients and non-transplant recipients, which studied prognostic factors in COVID-19 using a matched propensity score, showed that neither being transplanted nor taking immunosuppressants was an independent prognostic factor. However, age over 65 years, creatinine and CRP levels during infection were independent prognostic factors [12]. It is also worth noting that another prognostic factor among transplant recipients was the time of infection during the pandemic. In the Spanish series, as progress was made in understanding the virus, its timeline, in optimizing active or useless drugs, as it could be diagnosed better and earlier, patients were better placed, admitted less frequently to critical care, suffered less ADRS and their mortality decreased [10].

Among patients with hematopoietic malignancies undergoing hematopoietic stem cell transplantation (HSCT), the median time from transplantation to COVID-19 infection was 17 months for allogeneic HSCT recipients and 23 months for autologous HSCT recipients. Fifteen percent in both groups developed severe disease requiring mechanical ventilation. Overall survival for both groups was 68%. Being aged 50 years or older, being male or developing COVID-19 infection within 12 months post-transplant were associated with an increased risk of mortality among allogeneic HSCT recipients. A diagnosis of lymphoma was associated with an increased risk of mortality compared to plasma cell dysplasia or myeloma in autologous recipients [13].

## **PATHOGENESIS OF SARS-COV-2 INFECTION. RELATIONSHIP TO GRAFT-MEDIATED TRANSMISSION**

At the beginning of the pandemic in 2020, detection of SARS-CoV-2 RNA by RT-PCR (*real time protein chain reaction*) was reported in blood (8-15%) and in feces (50%) of patients infected by COVID-19. Also, in *postmortem* studies coronavirus-like inclusions were found in kidney [14-15]). This triggered a universal fear of transplanting organs from donors with suspected or confirmed SARS-CoV-2 infection. Eventually reassuring evidence began to emerge. In China, they detected viremia in only 0.1% of convalescent COVID blood donors, being more likely to be detected in those patients with more severe disease [16]. Also, subsequent studies in cardiac donors with positive PCR at the time of donation failed to detect SARS-CoV-2 in cardiac tissues [17].

Microbiological studies correlated the time at which the detectable virus had no infectious capacity in cell cultures [18], which associated with knowledge of the incubation period and that of symptoms (only 100 out of every 10,000 cases developed symptoms after 14 days [19], made it possible to establish the time of lowest infectious risk in convalescent donors. Thus, if a donor had died 14-21 days after the onset of symptoms, had remained asymptomatic in the last 72 hours and the result of the molecular study (PCR) against SARS-CoV-2 was negative, he could be a donor according to the recommendations of scientific societies, such as the Spanish Transplant Organization (ONT) [20].

However, in clinical practice, the PCR result could be positive for more than 3 weeks in convalescent or clinically resolved patients. Therefore, it was necessary to discriminate which PCR amplification cycle (the Ct or "cycle threshold") could be a surrogate marker of viral viability. In other words, at what Ct there was no longer any growth or cytopathic effect in cell cultures. The first studies placed it at 24 [18,19], although later publications would raise it above 28 [21] and finally above 30 in lower respiratory samples from patients hospitalized in the critical care unit [22]. With these two parameters (more than 14 clinical days and a Ct above 30 in the PCR study) and considering the limitation generated by the variability existing between the different studies reported on infectivity/virulence, the first review study appeared in which no case of SARS-CoV-2 transmission by cell, tissue or organ transplantation was documented [23]. Except for the lung and intestine, some clinical studies, which we will discuss below, have been able to confirm this.

Finally, two other parameters were also assessed individually in the transmission risk screening: the clinical category of severity with which the donor had been infected before death, classified as mild (at home), moderate (hospitalized medical wards) or severe (in the critical care unit), and the presence of IgG antibodies to SARS-CoV-2, which could give an idea of the immune response.

With the parameters described above and knowing that more COVID-infected patients with terminal organ failure were hospitalized and died on the waiting list than transplant recipients convalescing from the infection [24,25], especially in the case of liver and kidney transplantation, a justification was found to reactivate donation and transplantation activity.

## **IMPACT OF COVID-19 VACCINATION ON DONATION AND TRANSPLANT**

The response to immunization in transplant recipients and the risk of acquiring infection after transplantation has been an obsession for transplant teams. Undoubtedly, vaccination has been able to contain the impact of the pandemic in the world population and the transplanted population is no exception. However, the response to immunization is varied depending on whether we value natural or vaccinal immunization and whether we focus on the humoral or cellular response.

The natural cellular response (that acquired after infection) is maintained after transplantation. A small study of 23 infected transplant recipients monitored at 4 and 6 months maintained TCD4 and TCD8 responses as measured by intracellular cytokine staining [26]. This response was also maintained in another group of 31 liver transplant recipients who also had their TCD4 and TCD8 response and fluorospot (IFN- $\gamma$ ) determined [27].

Vaccine immune response in the transplanted patient is not as consistent. A meta-regression analysis of 27 studies evaluated the humoral and cellular response in 1,452 renal transplant patients after vaccination against COVID-19 (all

were seronegative before vaccination). The humoral response was significantly lower, with a gradual increase to 29.98% at week 4 post-vaccination, with the control group maintaining 98%. The cellular response increased from 5% to 59.84%, being higher than 90% in the control group [28]. Another prospective analysis of the immune response at 6 months in 200 patients undergoing SOT (Liver 61 (30.5%), Kidney 102 (51%), Lung 37 (18.5%)) versus 200 healthy controls, showed a humoral response of 36% in the transplanted population versus 97.5% in the control population. The cellular response was performed by measuring interferon- $\gamma$  (IFN- $\gamma$ ) after whole blood stimulation with SARS-CoV-2 S1 antigen. This response was 13.1% in transplant recipients versus 59.4% in the control group [29].

The median humoral response, measured by antibody determination after mRNA vaccines (e.g., BNT162b2) was 30%-40% depending on published series. In renal transplantation from 30% to 60% [30-32], in liver transplantation from 40% to 60% [30,33,34] and from 10% to 40% in lung transplantation [30,35].

Transplant patients were considered a priority in vaccination programs against SARS-CoV-2. In the same way, vaccination of patients on the transplant waiting list should be prioritized, although not delaying a transplant opportunity because they have not completed a vaccination schedule. Patients on the transplant waiting list should have their vaccination schedule updated to the epidemiological situation in their environment. Vaccination is also indicated in those patients who have passed COVID-19 or who have a positive serostatus against SARS-CoV-2. In the case of patients who have passed the infection (symptomatic or asymptomatic), guidelines indicated by the health authorities should be followed. Vaccination schedules do not differ from those used in the general population. These vaccines have proven to be safe, although they lose effectiveness over time, to a lesser extent than those of viral vectors, especially against new variants such as omicron [36,37]. This type of RNA vaccine avoids possible alloreactivity phenomena that could have an impact on the transplanted organ. Since there are no studies that define the time of vaccination indication in recently transplanted patients and by analogy with other vaccination strategies against respiratory viruses, vaccination could begin from the first month in the case of solid organ recipients and between three and six months in hematopoietic precursor recipients.

Perhaps the most important thing after taking a measure is to evaluate it. What is the risk of acquiring SARS-CoV-2 infection in vaccinated transplant recipients, and what impact does it have? An United Kingdom retrospective study evaluated the effectiveness of the vaccine in SOT patients in 43,481 transplant recipients aged 16 years and older with full vaccination schedules between September 2020 and August 2021. The vaccines included were Pfizer BioNTech (BNT162b2) and Oxford-Astra-Zeneca (ChAdOx1-S), the predominant variants in the study were Alpha (B.1.1.7) and Delta (B.1.617.2). Of the 43,481 patients, 3,080 were unvaccinated, 1,141 had 1 dose and 39,260 had 2 doses. 4147 (9.53%) were infected, 2,575 of

them (83.6%) were not vaccinated, 258 (22.6%) had received 1 dose and 1314 (3.35%) 2 doses. Seventy percent were renal transplant recipients and infection occurred more than one year after transplantation. Of those infected, a total of 407 (9.8%) died on day 28, 269 (10.4%) were not vaccinated, 30 (11.6%) had received 1 dose and 108 (8.2%) had received 2 doses. Vaccination resulted in a 20% reduction in the risk of death in SOT patients ( $p=0.05$ ) (HR mortality up to day 28 after infection = 0.80 (0.63 - 1.00)). Although this risk reduction is significant, it is lower in the unvaccinated population (90%). Vaccination was not associated with a lower risk of infection (IRR= 1.29 (1.03 - 1.61)) [38]. Another Greek study evaluated the clinical outcomes of SARS-CoV-2 infection in relation to humoral response in fully vaccinated SOT recipients (at least 14 days after second dose). A total of 449 vaccinated SOTs (with more than one comorbidity, more than one year of transplantation and their immunosuppressive treatment) were included. A total of 15 were infected (3.34%) and at that time 6 (40%) were seropositive and 9 (60%) seronegative (< threshold 50 AU/mL). Of the 15 infected 8 were admitted, 7 had severe disease and 2 died [39]. Finally, a third North American, retrospective multicenter study evaluated the risk of infection after vaccination and compared it with the general population. It analyzed 18,215 fully vaccinated SOT patients. A total of 151 (0.83%) were infected, 87 of these (57.6%) required hospitalization and 14 (9.3%) died. The conclusion reached by the authors is that transplant patients have less post-vaccination protection than the general population and that they should continue with barrier measures [40]. This condition of lower protection should have implications for treatment.

## EVOLUTION OF DONATION IN SPAIN THROUGHOUT THE PANDEMIC

As in other countries, the situation of donation and transplantation in Spain changed according to changes in the development of the pandemic (waves and variants) and the accumulated scientific evidence. Thus, 2020 was characterized by diagnosis, 2021 by vaccination and 2022 by the start of treatment.

Between March and December 2020 (first and second waves), an increase in the incidence and mortality from COVID-19 began to be observed worldwide, especially in the transplanted population. The international medical community, concerned about the decrease in healthcare resources dedicated to care and the fear of transmission during donation or post-transplant recipient infection, decided to suspend donation and transplantation. Activity was only maintained with death brain donors (DBD) or death cardiac donors (DCD) after withdrawing life-sustaining therapies (WLSTs), in low incidence geographic areas, and after screening with 2 separate PCR tests 24-48 hours apart. Uncontrolled DCD (type II of Maastricht) was discontinued. Protocols were proposed for the transport of potential donors between centers looking for those with lower incidence or greater availability of beds (using continuous veno-venous haemofiltration techniques, ECMO, etc).

Between January and May 2021 (third and fourth waves) there were fewer admissions and mortality in transplant recipients with COVID than in the first wave, there was better diagnostic capacity, vaccination programs were developed worldwide, and scientific evidence allows optimization of remdesivir, dexamethasone, oxygen therapy and anti-inflammatory monoclonal antibodies (tocilizumab, baricitinib). Safety algorithms began to be generated to weigh the risk of COVID transmission (intensity of the disease, time to donation, replicative capacity of the virus at the time of donation measured by the Ct of the PCR, if positive). All this allowed initiation of DCD and DBD activity. The uncontrolled DCD remained suspended.

Between June 2021 and March 2022 (fifth and sixth waves and after) the delta variant was predominant until December and then omicron subvariants (B.A 1, B.A 2, B.A 4/5). The infection rate was higher, although with fewer hospitalizations due to the lower aggressiveness of the strain and vaccine implementation (85-90% of the population). The development of new antiviral drugs such as molnupiravir and nirmatrelvir/ritonavir and monoclonal antibodies such as sotrovimab or casirivimab/imdevimab was completed. The first series of patients transplanted from donors with positive PCR appeared, with informed consent and good results, except in lung transplantation. However, donation and transplantation took a long time to take off for logistical reasons: numerous sick leaves and exhausted among healthcare workers due to work overload, limited availability of beds, the surgical activity No COVID, delayed during the pandemic, competed with the resources of the operating room or critical care beds and there was also a turnover of personnel in all areas (doctors, nurses, assistants, etc.) with less awareness of donation. With all this, donation continues from DCD and DBD if the hospital logistics allow it, and the DCD uncontrolled with triple safety screening (out-of-hospital donor nasal antigen, family questionnaire on COVID and PCR on arrival of the donor at the emergency room) begins to be activated.

Even though donation and transplantation figures are still closer to those of 2017, the report issued by ONT as of January 27th, 2022, reflected an overall growth of 7% in all types of transplantation (1,905 donors, (40.2 donors per million population (pmp) with 4,781 transplants (101 pmp transplants) of which 159 transplants have been to children). On the other hand, 26,347 new bone marrow donors were registered, meaning that our country now has 452,552 registered donors, in line with the objectives of the third phase of National Bone Marrow Plan. At the other extreme is the waiting list, which stands at 4,762 patients, 66 of them of pediatric age. In 2020 the list was 4,794 patients, 92 of them of pediatric age [41].

## LESSONS LEARNED AND EXPERIENCE IN SARS-CoV-2-INFECTED DONOR RECIPIENTS

There are published references on the absence of SARS-CoV-2 transmission in organ recipients from donors convalescing from infection with 2 months or more prior to donation [42,43]. However, much more relevant is the increasing

communication of series demonstrating the absence of SARS-CoV-2 transmission from donors with positive PCR at the time of donation, with ranges from 0 to 30 days from PCR positivity to renal [44,45], hepatic [44,46-48], and cardiac [44,49] donation. However, the results were not similar in lung donation. Of 3 lung implants from positive PCR for SARS-CoV-2 donors (with negative nasopharyngeal PCR and positive bronchioalveolar lavage PCR), 3 developed critical illness and 1 died [50,51].

In the analysis of the cohort of 17,694 donors from the American national database (OPTN), 150 were positive for SARS-CoV-2. Of these, 269 organs were transplanted, including 187 kidneys, 57 livers, 18 hearts, 5 kidney-pancreas, and 2 lungs. The median time from COVID-19 testing to donation was 4 days for positive donors. Survival of patients who received grafts from COVID-19-positive donors and complications of graft dysfunction were equivalent to those who received grafts from COVID-19-negative donors [52]. Similar results were reported by Dhand et al. with 193 COVID+ donors resulting in the transplantation of 281 kidneys, 106 livers and 36 hearts in 414 adult recipients [53]. A systematic review conducted with published from January 2019 to December 2021 collected information from sixty-nine recipients who received 48 kidneys, 18 livers, and 3 hearts from 57 donors with positive RT-PCR for SARS-CoV-2. The investigators concluded that the use of nonpulmonary organs (kidney, liver, and heart) from SARS-CoV-2 positive donors appeared to be a safe practice, with a low risk of transmission, regardless of the presence of symptoms at the time of procurement [54]. Finally, a bioethical analysis addressing the four issues that are considered to constitute the essential structure of individual clinical cases for ethical analysis (medical indications, patient preferences, quality of life and contextual characteristics) concluded that the decision to perform liver transplantation in selected patients shows that the decision is ethically justifiable [55].

In an interesting report, Eichenberger EM et al [56] summarize the lessons learned about donation and transplantation in relation to COVID and could be summarized as follows:

- In non-pulmonary donors (kidney, liver, heart, or pancreas), even with unknown time since infection, without severe disease, no transmission has occurred. Intestinal transplantation is also not indicated due to prolonged viral shedding, which often exceeds 50 days.
- Donors with critical COVID-19, even non-pulmonary, may have organ quality problems due to microvascular disease. Biopsy should be considered in these cases.
- Patients on the waiting list with end-stage organ disease or those with high morbidity might be considered for organ transplantation from a COVID-19-positive donor.
- Recipients should be vaccinated, and transplant teams should encourage vaccination.
- Recipient informed consent should be obtained well in advance of transplantation.
- Although SARS-CoV-2 RNA could be detected in any organ, there is no viable or transmissible virus in organs other than the bowel or lung.

- Most recipients underwent treatment for COVID-19 with remdesivir, neutralizing antibodies or both since there is authorization for its use in transplant recipients.

## MAIN THERAPEUTIC TOOLS APPROVED IN THE TREATMENT OF INFECTION. APPLICABILITY IN TRANSPLANT PATIENTS

Given the morbidity and mortality associated with SARS-CoV-2 infection in transplant recipients. It would be advisable to assess the specific treatment alternatives that could benefit these patients. Although experience is limited, some alternatives are presented.

**Remdesivir.** Remdesivir is a direct-acting nucleotide prodrug of SARS-CoV-2 RNA-dependent RNA polymerase. It has potent activity in primary airway epithelial cells. A phase 3 trial of remdesivir demonstrated that both a 5- and 10-day schedule shortened recovery time in hospitalized patients with COVID-19 [57,58]. Shorter treatment regimens (3 days) have prevented progression to severe disease in ambulatory patients with good adherence and tolerance [59]. In a small Italian case series of 24 patients, 7 treated with remdesivir versus 17 placebo, the authors recognize the usefulness of this same scheme in solid organ recipients, avoiding disease progression and ICU admission [60]. It is currently the most widely used antiviral in the infection of hospitalized transplant recipients, alone or in combination with sotrovimab.

**Nirmatrelvir/ritonavir.** This is a new orally bioavailable protease inhibitor, which has demonstrated activity against SARS-CoV-2. In a recent phase 2/3 clinical trial in 2,246 SARS-CoV-2 infected patients, Nirmatrelvir (co-administered with ritonavir 100 mg twice daily) reduced the risk of hospitalization or death by 89% compared to placebo [61]. The main problem associated with prescribing this antiviral in the SOT population is that ritonavir is a potent cytochrome P450 (CYP) 3A inhibitor and poses significant drug-drug interaction problems, especially with anticalcineurin drugs. In addition, nirmatrelvir/ritonavir requires dose adjustment in renal insufficiency and its use is not recommended in patients with a clearance of less than 30 ml/min. There is some brief communication in which some precautions for its use are recommended, knowing the interindividual variability in the metabolic activity of P450 (CYP) 3a. Lange et al [62] recommend starting nirmatrelvir/ritonavir from day 1 to day 5. Maintain tacrolimus from day 1 to 5 (do levels on day +3 in case the dose needs to be adjusted). In the case of cyclosporine, reduce the dose to 80% of the usual dose. On day 6-7 do levels of tacrolimus or cyclosporine. In the case of tacrolimus, if the levels are suprathereapeutic, maintain the dose and repeat after 2-4 days. If the levels are therapeutic, initiate treatment at a dose of 25-50% of the usual dose and repeat after 2-4 days. If subtherapeutic, start treatment at a dose of 25-75% of the usual dose and repeat after 2-4 days. In the case of cyclosporine, if levels are suprathereapeutic, reduce the dose. In other interaction models, cyclosporine has been reduced to 20% of the usual dose. Repeat levels after 2-4 days. If levels are therapeutic, continue and monitor again

after 2-4 days. If they are subtherapeutic, the dose should be increased, repeating the dose after 2-4 days. This proposal is indicative. In the case of other concomitant medication such as azoles, anticoagulants, this regimen should be individualized. Other researchers [63] propose reintroducing tacrolimus in partial or full doses between days 8 and 10, ideally guided by drug levels. To avoid elevation of transaminases, it may be prudent to discontinue statins on the day of initiation of treatment.

**Molnupiravir.** It is a derivative of the synthetic nucleoside N4-hydroxycytidine that exerts its antiviral action through the introduction of copy errors during viral RNA replication, which has been shown to reduce hospitalization and death in SARS-CoV-2 infection [64]. Molnupiravir provides some advantages for use in transplant patients. Since it has low affinity for CYP 3 A (P450), it does not interact with the metabolism of anticalcineurin drugs, as happens with ritonavir. Furthermore, it does not require dose adjustment in patients with renal insufficiency, as is the case with nirmatrelvir/ritonavir or remdesivir. Finally, being an oral drug, it facilitates compliance, sequential therapy after remdesivir or combination therapy. There is little experience in renal transplant recipients with molnupiravir in the early treatment of SARS-CoV-2 infection. In a small Spanish comparative study, no differences were found between molnupiravir (4 patients) and remdesivir (9 patients) in survival, tolerance or poor clinical course, even in very immunosuppressed patients (methylprednisolone bolus, basiliximab, antithymocyte gamma globulin) [65]. In a retrospective American series, the 49 transplanted patients infected with SARS-CoV-2 during the omicron variant and treated with molnupiravir had less hospitalization and death. Four of them had minor side effects (2 rash and 2 gastrointestinal complaints) [66].

**Sotrovimab.** Monoclonal antibodies have been shown to reduce hospitalization, ICU admission and mortality due to COVID-19 and would be especially useful, alone or in association with specific antiviral treatment, in the immunosuppressed or comorbid population. The most commonly used antibodies in 2021 and 2022 have been casirivimab-imdevimab and sotrovimab. Specifically in solid organ transplant recipients, two studies, with 35 and 28 patients treated with monoclonal antibodies, reduced hospitalization and ICU admission in transplant recipients infected with Delta variant, with no mortality [67,68]. However, the neutralizing capacity of monoclonal antibodies varies according to the viral variants. Thus, there are areas of greater variability in the RBD (receptor binding domain) of viral spike, that modify this "anchor zone" of the monoclonal antibody in the mutational variants, making it less neutralizing. There is an *in vitro* neutralization reference from Stanford University [69] that periodically updates the neutralization capacity of the different synthetic monoclonal antibodies, although there are no references that correlate that *in vitro* neutralization quotient with the greater or lesser beneficial effect *in vivo* or the neutralization breakpoint at which a therapeutic monoclonal antibody should be rejected. In addition, there is also an effect, termed "effector function" that recruits cells of the immune system to facilitate the elim-

ination of infected cells [70]. It is not known whether this is a constant class effect for all monoclonal antibodies or whether it is more intense in some or in others, but even with a reduction in the neutralizing threshold according to the Stanford references, some monoclonal antibodies are able to reduce viral load in experimental models [71].

These modifications in RBD referred above change with the viral variant. For example, after selection of Delta strain and the reduction of the neutralization capacity according to the Stanford references, two antibodies (etesivimab or bamlanivimab) were withdrawn from the market, leaving casirivimab/imdevimab and sotrovimab as the only active drugs. After selection Omicron, casirivimab/imdevimab was also no longer recommended for the same reason. A prospective multicenter real-life cohort study of patients treated with casirivimab/imdevimab (n= 133 vs. Delta) or sotrovimab (n= 116 vs. Omicron), in which 40% were solid organ recipients, has been published with results of reduced hospitalization and ICU admission, and no mortality [72]. A French retrospective observational study conducted between March and June 2021 compared the clinical course of 80 renal transplant recipients treated with sotrovimab for SARS-CoV-2 infection against 155 patients undergoing standard of care. Of the 80 patients treated with the monoclonal antibody, 3 (3.8%) required hospital admission, 2 (2.5%) required ICU admission, none required mechanical ventilation and there were no deaths. In the control group 30 patients (19.4%) were admitted, 24 (15.5%) were admitted to ICU, 18 (11.6%) required mechanical ventilation and all 18 (11.6%) died. All comparisons reached statistical significance [73]. A retrospective study compared the clinical outcomes of the first 25 renal transplant patients treated with sotrovimab against mild-moderate Omicron BA.1 infection versus 100 renal transplant patients who received only the standard of care. In the sotrovimab arm (n = 25) there were 4 hospitalizations (16%), 1 patient was admitted to the ICU, and no deaths. In the standard-of-care arm (n = 100) there were 35 hospitalizations (35%), 17 patients were admitted to ICU (17%), and 11 died (11%) [74].

Omicron variant has also undergone mutations in RBD, changing from BA.1 to BA.2 and currently also to BA.4/5. This has correlated with modifications in the Stanford neutralization standards, leaving sotrovimab and the combination of tixagevimab/cilgavimab as the only recommended monoclonal antibodies. Results of a study comparing the activity of sotrovimab among high-risk BA.1 vs. BA.2 variant-infected patients have recently been reported. In this study, of the 47 BA.2-infected patients, at least 35 were high-risk immunosuppressed (steroid therapy, solid organ or hematopoietic transplantation, chemotherapy, or rituximab immunotherapy). Although the sample size was relatively small, sotrovimab was associated with a low incidence of COVID-19-related hospitalization or death in this very high-risk population with mild to moderate SARS-CoV-2 infection and no new mutations [75]. Sotrovimab is currently an effective alternative, associated with the standard of care to prevent progression of SARS-CoV-2 infection in high-risk patients, such as transplant recipients.

## CONFLICT OF INTEREST

Authors declare no conflict of interest

## REFERENCES

- Petrilli CM, Jones SA, Yang J, Rajagopalan H, et al. "Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study". *BMJ* 2020; 369:m1966.
- World Health Organization, Clinical Management of COVID-19 (accessed august 2022).
- National Institutes of Health, COVID-19 Treatment Guidelines (accessed august 2022).
- Bonnad C, García-Blas S, Tarazona-Santabalbina F, Sanchis J, Bertomeu-González V, Fácila L, et al. The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects. *J Am Med Dir Assoc.* 2020; 21(7): 915-918.
- Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect.* 2020; 81(2): e16-e25.
- World Health Organization. Statement on tobacco use and COVID-19 (accessed august 2022).
- Nandy K, Salunke A, Pathak SK, Pandey A, Doctor C, Puj K, et al. Coronavirus disease (COVID-19): A systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. *Diabetes Metab Syndr.* 2020 Sep-Oct;14(5):1017-1025.
- Kates OS, Haydel BM, Florman SS, et al. Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study. *Clin Infect Dis.* 2021; 73: e4090-e4099.
- Kute VB, Bhalla AK, Guleria S, et al. "Clinical Profile and Outcome of COVID-19 in 250 Kidney Transplant Recipients: A Multicenter Cohort Study From India". *Transplantation.* 2021; 105 (4): 851-860.
- Coll E, Fernández-Ruiz M, Padilla M, Moreso F, Hernández-Vicente A, Yañez I, et al. "Spanish Group for the Study of COVID-19 in Transplant Recipients. COVID-19 in Solid Organ Transplant Recipients in Spain Throughout 2020: Catching the Wave?" *Transplantation.* 2021; 105 (10): 2146-2155.
- Caillard S, Chavarot N, Francois H, Matignon M, Greze C, Kamar N, et al on behalf of French SOT COVID Registry. Is COVID-19 infection more severe in kidney transplant recipients? *Am J Transplant.* 2021 Mar;21(3):1295-1303. doi: 10.1111/ajt.16424.
- Linares L, Cofan F, Diekmann F, Herrera S, Marcos MA, Castel MA, et al from Hospital Clínic COVID-19 research group. A propensity score-matched analysis of mortality in solid organ transplant patients with COVID-19 compared to non-solid organ transplant patients. *PLoS One.* 2021; 16(3): e0247251.
- Sharma A, Bhatt NS, St Martin A, Abid MB, Bloomquist J, Chemaly RF, et al. Clinical characteristics and outcomes of COVID-19 in hematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol.* 2021; 8(3): 185-e193.
- Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al

- on behalf of Singapore 2019 Novel Coronavirus Outbreak Research Team. "Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore". *JAMA*. 2020; 323(15): 1488-1494.
15. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020; 98(1): 219-227.
  16. Chang L, Zhao L, Gong H, Wang L, Wang L. Severe Acute Respiratory Syndrome Coronavirus 2 RNA Detected in Blood Donations. *Emerg Infect Dis*. 2020 Jul;26(7):1631-1633. doi: 10.3201/eid2607.200839.
  17. Ashari R, Van Esbroeck M, Vanhaebost J, Micalessi I, Kerschen A, Mastrobuoni S. The risk of transmission of the novel coronavirus (SARS-CoV-2) with human heart valve transplantation: evaluation of cardio-vascular tissues from two consecutive heart donors with asymptomatic COVID-19. *Cell Tissue Bank*. 2021 Dec;22(4):665-674. doi: 10.1007/s10561-021-09913-z.
  18. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples. *Clin Infect Dis*. 2020; 71(10): 2663-2666
  19. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med*. 2020; 172(9): 577-582.
  20. Domínguez-Gil B, Fernández-Ruiz M, Hernández D, Crespo M, Colmenero J, Coll E et al. Organ Donation and Transplantation During the COVID-19 Pandemic: A Summary of the Spanish Experience. *Transplantation* 2021; 105: 29-36.
  21. Kim MC, Cui C, Shin KR, Bae JY, Kweon OJ, Lee MK, et al. Duration of Culturable SARS-CoV-2 in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021; 384(7): 671-673.
  22. Folgueira MD, Luczkowiak J, Lasala F, Pérez-Rivilla A, Delgado R. Prolonged SARS-CoV-2 cell culture replication in respiratory samples from patients with severe COVID-19. *Clin Microbiol Infect*. 2021; 27(6): 886-891.
  23. Gausson A, Hornby L, Rockl G, O'Brien S, Delage G, Sapir-Pichhadze R, et al. Evidence of SARS-CoV-2 Infection in Cells, Tissues, and Organs and the Risk of Transmission Through Transplantation. *Transplantation*. 2021; 105(7): 1405-1422.
  24. Ravanan R, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: A national cohort study. *Am J Transplant*. 2020 Nov;20(11):3008-3018. doi: 10.1111/ajt.16247.
  25. Craig-Schapiro R, Salinas T, Lubetzky M, Abel BT, Sultan S, Lee JR, et al. COVID-19 outcomes in patients waitlisted for kidney transplantation and kidney transplant recipients. *Am J Transplant*. 2021 Apr;21(4):1576-1585. doi: 10.1111/ajt.16351.
  26. Fernández-Ruiz M, Olea B, Giménez E, Laguna-Goya R, Trujillo H, Caravaca-Fontán F, et al. SARS-CoV-2-specific Cell-mediated Immunity in Kidney Transplant Recipients Recovered From COVID-19. *Transplantation*. 2021 Jun 1;105(6):1372-1380. doi: 10.1097/TP.0000000000003672.
  27. Fernández-Ruiz M, Olea B, Almendro-Vázquez P, Giménez E, Marcacuzco A, San Juan R, et al. T cell-mediated response to SARS-CoV-2 in liver transplant recipients with prior COVID-19. *Am J Transplant*. 2021 Aug;21(8):2785-2794. doi: 10.1111/ajt.16708.
  28. Swai J, Gui M, Long M, Wei Z, Hu Z, Liu S. Humoral and cellular immune response to severe acute respiratory syndrome coronavirus-2 vaccination in haemodialysis and kidney transplant patients. *Nephrology (Carlton)* 2022;27(1):7-24. Doi:10.1111/nep.13974
  29. Hamm SR, Møller DL, Pérez-Alós L, Hansen CB, Pries-Heje MM, Heftdal LD, et al. Decline in antibody concentration 6 months after two doses of SARS-CoV-2 BNT162b2 vaccine in solid organ transplant recipients and healthy controls. *Front Immunol*. 2022;13:832501. doi:/10.3389/fimmu.2022.832501
  30. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA*. 2021 Jun 1;325(21):2204-2206. doi: 10.1001/jama.2021.7489..
  31. Crespo M, Barrilado-Jackson A, Padilla E, Eguía J, Echeverría-Esnal D, Cao H, et al. Negative immune responses to two-dose mRNA COVID-19 vaccines in renal allograft recipients assessed with simple antibody and interferon gamma release assay cellular monitoring. *Am J Transplant*. 2022 Mar;22(3):786-800. doi: 10.1111/ajt.16854.
  32. Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, Casals-Urquiza J, et al. Cellular and humoral response after MRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. *Am J Transplant*. 2021 Aug;21(8):2727-2739. doi: 10.1111/ajt.16701.
  33. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol*. 2021 Aug;75(2):435-438. doi: 10.1016/j.jhep.2021.04.020.
  34. Ruether DF, Schaub GM, Duengelhoefer PM, Haag F, Brehm TT, Fathi A, et al. SARS-CoV-2-specific Humoral and T-cell Immune Response After Second Vaccination in Liver Cirrhosis and Transplant Patients. *Clin Gastroenterol Hepatol*. 2022 Jan;20(1):162-172.e9. doi: 10.1016/j.cgh.2021.09.003.
  35. Shostak Y, Shafran N, Heching M, Rosengarten D, Shtraichman O, Shitenberg D, et al. Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine. *Lancet Respir Med*. 2021 Jun;9(6):e52-e53. doi: 10.1016/S2213-2600(21)00184-3.
  36. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning Immunity after the BNT162b2 Vaccine in Israel. *N Engl J Med*. 2021; 385(24): e85.
  37. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet*. 2022; 399(10328): 924-944.
  38. Callaghan CJ, Mumford L, Curtis RMK, Williams SV, Whitaker H, Andrews N, et al. Real-world effectiveness of the Pfizer-BioNTech BNT162b2 and oxford-AstraZeneca ChAdOx1-S vaccines against SARS-CoV-2 in solid organ and islet transplant recipients. *Transplantation*. 2022;106(3):436-46. Doi: 10.1097/TP.0000000000004059

39. Marinaki S, Xagas E, Tsoutsoura P, Katsaros D, Korogiannou M, Boletis IN. Occurrence of Severe SARS-CoV-2 Infection in Fully Vaccinated Solid Organ Transplant Recipients. *Transplant Proc.* 2021 Dec 31; 50(41-1345(21))00941-6. doi: 10.1016/j.transproceed.2021.12.012.
40. Qin CX, Moore LW, Anjan S, Rahamimov R, Sifri CD, Ali NM, et al. Risk of Breakthrough SARS-CoV-2 Infections in Adult Transplant Recipients. *Transplantation.* 2021 Nov 1;105(11): e265-e266. doi: 10.1097/TP.0000000000003907.
41. Balance de actividad Donación y Trasplante 2021 de la ONT, disponible en <http://www.ont.es/infesp/Paginas/Memorias.aspx>
42. Neidlinger NA, Smith JA, D'Alessandro AM, Roe D, Taber TE, Pereira MR, Friedman AL. Organ recovery from deceased donors with prior COVID-19: A case series. *Transpl Infect Dis.* 2021 Apr;23(2):e13503. doi: 10.1111/tid.13503.
43. Kute VB, Godara S, Guleria S, Ray DS, Aziz F, Hegde U et al. Is it Safe to Be Transplanted From Living Donors Who Recovered From COVID-19? Experience of 31 Kidney Transplants in a Multicenter Cohort Study From India. *Transplantation.* 2021 Apr 1;105(4):842-850. doi: 10.1097/TP.0000000000003609.
44. Sigler R, Shah M, Schnickel G, Pretorius V, Dan J, Taremi M, Aslam S. Successful heart and kidney transplantation from a deceased donor with PCR positive COVID-19. *Transpl Infect Dis.* 2021 Oct;23(5): e13707. doi: 10.1111/tid.13707.
45. Koval CE, Poggio ED, Lin YC, Kerr H, Eltemamy M, Wee A. Early success transplanting kidneys from donors with new SARS-CoV-2 RNA positivity: A report of 10 cases. *Am J Transplant.* 2021 Nov;21(11):3743-3749. doi: 10.1111/ajt.16765.
46. Dhand A, Gass A, Nishida S, Kai M, Berger K, Wolf D, et al. Successful transplantation of organs from a deceased donor with early SARS-CoV-2 infection. *Am J Transplant.* 2021 Nov;21(11):3804-3805. doi: 10.1111/ajt.16706.
47. Kulkarni AV, Parthasarathy K, Kumar P, Sharma M, Reddy R, Chaitanya Akkaraju Venkata K, et al. Early liver transplantation after COVID-19 infection: The first report. *Am J Transplant.* 2021 Jun;21(6):2279-2284. doi: 10.1111/ajt.16509.
48. Romagnoli R, Gruttadauria S, Tisone G, Maria Ettorre G, De Carlis L, Martini S, et al. Liver transplantation from active COVID-19 donors: A lifesaving opportunity worth grasping? *Am J Transplant.* 2021 Dec;21(12):3919-3925. doi: 10.1111/ajt.16823.
49. de la Villa S, Valerio M, Salcedo M, Ortiz-Bautista C, Catalán P, Padilla B, et al. Heart and liver transplant recipients from donor with positive SARS-CoV-2 RT-PCR at time of transplantation. *Transpl Infect Dis.* 2021 Oct;23(5): e13664. doi: 10.1111/tid.13664.
50. Kaul DR, Valesano AL, Petrie JG, Sagana R, Lyu D, Lin J, et al. Donor to recipient transmission of SARS-CoV-2 by lung transplantation despite negative donor upper respiratory tract testing. *Am J Transplant.* 2021 Aug;21(8):2885-2889. doi: 10.1111/ajt.16532.
51. Kumar D, Humar A, Keshavjee S, Cypel M. A call to routinely test lower respiratory tract samples for SARS-CoV-2 in lung donors. *Am J Transplant.* 2021 Jul;21(7):2623-2624. doi: 10.1111/ajt.16576.
52. Bock MJ, Vaughn GR, Chau P, Berumen JA, Nigro JJ, Ingulli EG. Organ transplantation using COVID-19-positive deceased donors. *Am J Transplant.* 2022 Sep;22(9):2203-2216. doi: 10.1111/ajt.17145.
53. Dhand A, Okumura K, Nabors C, Nishida S. Solid organ transplantation from COVID positive donors in the United States: Analysis of United Network for Organ Sharing database. *Transpl Infect Dis.* 2022 Aug 9:e13925. doi: 10.1111/tid.13925.
54. Martinez-Reviejo R, Tejada S, Cipriano A, Karakoc HN, Manuel O, Rello J. Solid organ transplantation from donors with recent or current SARS-CoV-2 infection: A systematic review. *Anaesth Crit Care Pain Med.* 2022 Aug;41(4):101098. doi: 10.1016/j.accpm.2022.101098.
55. Grossi AA, Nicoli F, Cardillo M, Gruttadauria S, Tisone G, Ettorre GM, et al. Liver transplantation from active COVID-19 donors: Is it ethically justifiable? *Transpl Infect Dis.* 2022; 24(4): e13846. doi: 10.1111/tid.13846.
56. Eichenberger EM, Kaul DR, Wolfe CR. The pandemic provides a pathway: What we know and what we need to know about using COVID positive donors. *Transpl Infect Dis.* 2021 Oct 6: e13727. doi: 10.1111/tid.13727.
57. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med.* 2020; 383(19):1813-1826. doi: 10.1056/NEJMoa2007764
58. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med.* 2020; 383 (19):1827-1837. doi: 10.1056/NEJMoa2015301.
59. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al; GS-US-540-9012 (PINETREE) Investigators. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med.* 2022 Jan 27;386(4):305-315. doi: 10.1056/NEJMoa2116846.
60. Colaneri M, Amarasinghe N, Rezzonico L, Pieri TC, Segalini E, Sambo M, et al. Early remdesivir to prevent severe COVID-19 in recipients of solid organ transplant: a real-life study from Northern Italy. *Int J Infect Dis.* 2022; 121:157-160. doi: 10.1016/j.ijid.2022.05.001.
61. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med.* 2022 Apr 14;386(15):1397-1408. doi: 10.1056/NEJMoa2118542.
62. Lange NW, Salerno DM, Jennings DL, Choe J, Hedvat J, Kovac DB, et al. Nirmatrelvir/ritonavir use: Managing clinically significant drug-drug interactions with transplant immunosuppressants. *Am J Transplant.* 2022 Jul;22(7):1925-1926. doi: 10.1111/ajt.16955.
63. Wang AX, Koff A, Hao D, Tuznik NM, Huang Y. Effect of nirmatrelvir/ritonavir on calcineurin inhibitor levels: Early experience in four SARS-CoV-2 infected kidney transplant recipients. *Am J Transplant.* 2022 Aug;22(8):2117-2119. doi: 10.1111/ajt.16997.
64. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V et al; MOVE-OUT Study Group. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med.* 2022 Feb 10; 386(6):509-520. doi: 10.1056/NEJMoa2116044.
65. Villamarin M, Márquez-Algaba E, Esperalba J, Perelló M, Los Arcos I, Campany D, et al. Preliminary Clinical Experience of Molnupiravir to



- Prevent Progression of COVID-19 in Kidney Transplant Recipients. *Transplantation*. 2022 Aug 2; TP.0000000000004306. doi: 10.1097/TP.0000000000004306.
66. Radcliffe C, Palacios CF, Azar MM, Cohen E, Malinis M. Real-world experience with available, outpatient COVID-19 therapies in solid organ transplant recipients during the omicron surge. *Am J Transplant*. 2022 May 18;10.1111/ajt.17098. doi: 10.1111/ajt.17098.
  67. Yetmar ZA, Bhaimia E, Bierle DM, Ganesh R, Razonable RR. Breakthrough COVID-19 after SARS-CoV-2 vaccination in solid organ transplant recipients: An analysis of symptomatic cases and monoclonal antibody therapy. *Transpl Infect Dis* 2022;24(2): e13779. doi: /10.1111/tid.13779,
  68. Klein EJ, Hardesty A, Vieira K, Farmakiotis D. Use of anti-spike monoclonal antibodies in kidney transplant recipients with COVID-19: efficacy, ethnic and racial disparities. *Am J Transplant*. 2021;00:1–6. doi: 10.1111/ajt.16843.
  69. Coronavirus antiviral Et resistance database, Last updated on Sep 26, 2022, Available at: <https://covdb.stanford.edu/susceptibility-data/table-mab-susc/>
  70. Corti D, Purcell LA, Snell G, Vesler D. Tackling COVID-19 with neutralizing monoclonal antibodies. *Cell*. 2021; 184(12):3086–3108. doi: 10.1016/j.cell.2021.05.005
  71. Case JB, Mackin S, Errico JM, Chong Z, Madden EA, Whitener B, et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains. *Nat Commun*. 2022; 13(1):3824. doi: 10.1038/s41467-022-31615-7.
  72. Martin-Blondel G, Marcelin AG, Soulié C, Kaisaridi S, Lusivika-Nzinga C, Dorival C, et al; COCOPREV Study Group. Outcome of very high-risk patients treated by Sotrovimab for mild-to-moderate COVID-19 Omicron, a prospective cohort study (the ANRS 0003S COCOPREV study). *J Infect*. 2022 Jun;84(6): e101-e104. doi: 10.1016/j.jinf.2022.04.010.
  73. Gueguen J, Colosio C, Del Bello A, Scemla A, N'Guyen Y, Rouzaud C, et al. Early Administration of Anti-SARS-CoV-2 Monoclonal Antibodies Prevents Severe COVID-19 in Kidney Transplant Patients. *Kidney Int Rep*. 2022 Jun;7(6):1241–1247. doi: 10.1016/j.ekir.2022.03.020.
  74. Chavarot N, Melenotte C, Amrouche L, Rouzaud C, Sberro-Soussan R, Pavie J, et al. Early treatment with sotrovimab monoclonal antibody in kidney transplant recipients with Omicron infection. *Kidney Int*. 2022 Jun;101(6):1290–1293. doi: 10.1016/j.kint.2022.04.003.
  75. Martin-Blondel G, Marcelin AG, Soulié C, Kaisaridi S, Lusivika-Nzinga C, Dorival C, et al. Sotrovimab to prevent severe COVID-19 in high-risk patients infected with Omicron BA.2. *J Infect*. 2022; 85(4):e104–8. doi: 10.1016/j.jinf.2022.06.033.