

15. COVID- 19

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15.1 Clinical Features, Symptoms, and Outcomes

Kates, O. S., et al. (2021). Coronavirus disease 2019 in solid organ transplant: a multicenter cohort study. *Clinical Infectious Diseases*, 73(11), e4090–e4099. Retrieved from:

<https://doi.org/10.1093/cid/ciaa1097>

- Multicenter cohort study examining 28-day mortality of 482 solid organ transplant recipients (primarily kidney transplant recipients, 66%) diagnosed with COVID-19 early in the pandemic from March 1, 2020-April 15, 2020. This study found an overall mortality of 20.5%. Age and underlying conditions (congestive heart failure, chronic lung disease, abnormal chest imaging, obesity and lymphopenia) were predictors of mortality.

Pereira, M. R., et al. (2021). Outcomes of COVID-19 in solid organ transplant recipients: A matched cohort study. *Transplant Infectious Disease*, 23(4), e13637. Retrieved from:

<https://doi.org/10.1111/tid.13637>

- When compared to the general population, SOT recipients were more likely to receive COVID-19 specific therapies and to require ICU admission. Mortality (23.08% vs 23.14%, p=0.21) were not significantly different in SOT recipients hospitalized with COVID-19.

Danziger-Isakov, L., et al. (2021). Impact of COVID-19 in solid organ transplant recipients. *American Journal of Transplantation*, 21(3), 925–937. Retrieved from: <https://doi.org/10.1111/ajt.16449>

- Review article focusing on the impact of COVID-19 on donation, epidemiology, outcomes, treatment strategies, and transplantation as treatment for COVID-19.

Colmenero, J., et al. (2021). Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *Journal of Hepatology*, 74(1), 148–155. Retrieved from: <https://doi.org/10.1016/j.jhep.2020.07.040>

- In liver transplant patients, chronic immunosuppression increases the risk of acquiring COVID-19 but it could reduce disease severity. Complete immunosuppression withdrawal may not be justified. However, mycophenolate withdrawal or temporary conversion to calcineurin inhibitors or everolimus until disease resolution could be beneficial in hospitalized patients.

Azzi, Y., et al. (2021). COVID-19 and solid organ transplantation: a review article. *Transplantation*, 105(1), 37–55. Retrieved from: <https://doi.org/10.1097/TP.0000000000003523>

- Review article providing background of COVID-19 diagnosis, clinical features in general population as well as solid organ transplant recipients, outcomes summary for kidney, liver, heart and lung transplant recipients with COVID-19, donation during the pandemic, and treatment options.

Sharma, P., et al. (2021). COVID-19 outcomes among solid organ transplant recipients: A case-control study. *Transplantation*, 105(1), 128–137. Retrieved from: <https://doi.org/10.1097/TP.0000000000003447>

- High renal replacement therapy use was seen in SOT recipients, but the severe disease and short-term death were similar in both groups. Hydroxychloroquine for the treatment of COVID-19 among SOT recipients was associated with a 10-fold higher hazard of death compared to no hydroxychloroquine.

Myers, C. N., et al. (2020). COVID-19 in lung transplant recipients. *Transplant Infectious Disease*, 22(6), e13364. Retrieved from: <https://doi.org/10.1111/tid.13364>

- Case series of 8 lung transplant recipients. A short-term mortality of 25% was observed. 62.5% of patients developed infection within a year from induction, and both patients who died received basiliximab induction within the prior 2 weeks. 75% of patients improved or fully recovered, despite having moderate to severe disease requiring inpatient care. Recovered patients seem to have a preserved lung function. Most common presenting symptoms were dyspnea (75%), cough (75%), subjective fever (50%), and gastrointestinal symptoms (37.5%); only two patients (25%) had a measured fever (> 38.0 C degrees) on the day of diagnosis.

Molnar, M.Z., et al. (2020). Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. *Am J Transplant*. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7460925/>

- 28-day mortality in SOT patients was similar to non-SOT patients. There was no difference between groups in the duration of ICU length of stay, risk of ARDS, secondary infection, thromboembolic events, vasopressor use, or receipt or duration of invasive mechanical ventilation. SOT patients presented with more nasal congestion and diarrhea compared to non-SOT patients and had a 30% higher risk of AKI requiring RRT.

Gaston, D.C., et al. (2020). Clinical implications of SARS-CoV-2 cycle threshold values in solid organ transplant recipients. *Am J Transplant*. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7675520/>

- Retrospective chart review of 25 adult SOT recipients admitted to the Yale New Haven Health System between March 1 and May 15, 2020, analyzing 50 test results to investigate the clinical implications of SARS-CoV-2 C_T values in this population. Initial C_T values from upper respiratory tract samples were significantly higher in patients on tacrolimus but were not associated with admission severity nor highest clinical acuity. C_T values may not be useful to predict COVID-19 severity in SOT patients. SARS-CoV-2 C_T values may be more useful in informing infection prevention measures.

Roberts, M. B., et al. (2020). COVID-19 in solid organ transplant recipients: Dynamics of disease progression and inflammatory markers in ICU and non-ICU admitted patients. *Transplant Infectious Disease*, 22(5), e13407. Retrieved from: <https://doi.org/10.1111/tid.13407>

- SOT is associated with a high rate of hospitalization, ICU admission, and death from COVID-19 compared to data in the general population of patients with COVID-19. Despite reduction in immunosuppression, suspected rejection was rare. Hospitalized SOT recipients who require ICU admission are at significantly increased risk of co-infections compared to those who do not require ICU admission. The clinical course and trend of laboratory biomarkers is biphasic with a later, pronounced peak in inflammatory markers seen in those admitted to an ICU. CRP is a useful marker to monitor disease progression in SOT.

Elias, M., et al. (2020). COVID-19 infection in kidney transplant recipients: disease incidence and clinical outcomes. *J Am Soc Nephrol*; 31:2413–23. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7609004/>

- Patients with kidney transplants display a higher risk of mortality compared to the general population. Non-White ethnicity and comorbidities such as obesity, diabetes, asthma, and chronic pulmonary disease were associated with higher risk of developing COVID-19 disease in kidney transplant recipients.

Kim, M. Y., et al. (2020). General approach to the clinical care of solid organ transplant recipients with COVID-19 Infection: Management for transplant recipients. *Current Transplantation Reports*, 7(4), 366–378. Retrieved from: <https://doi.org/10.1007/s40472-020-00305-y>

- Transplant recipients should remain in close communication with their health team to monitor their overall health, manage comorbidities and identify any new findings that may confer risk of COVID-19. Finally, understanding of the transplant specific pathophysiology, effective treatments, and adjunctive practices for COVID-19 should be prioritized as part of a comprehensive research strategy to optimize outcomes.

15.2 Immune Response

Becchetti, C., et al. (2022). Humoral response to SARS-CoV-2 infection among liver transplant recipients. *Gut*, 71(4), 746–756. Retrieved from: <https://doi.org/10.1136/gutjnl-2021-326609>

- Prospective, multicenter case-control study examining antibodies to the nucleocapsid protein, spike (S) protein of SARS-CoV-2 and their neutralizing activity in 35 liver transplant recipients and matched controls including both immunocompetent patients as well as liver transplants without COVID-19 symptoms. It was found that despite being immunocompromised, liver transplant recipients were able to mount a detectable antibody response in 80% of cases, although that was significantly lower than the immunocompetent cohort ($p < 0.001$).

Morris, S., et al. (2022). Re-infection with SARS-CoV-2 in solid-organ transplant recipients: Incidence density and convalescent immunity prior to re-infection. *Transplant Infectious Disease*, 10.1111/tid.13827. Retrieved from: <https://doi.org/10.1111/tid.13827>

- Study of 210 solid organ transplant recipients who were infected with COVID-19 between March 1, 2020 and March 30, 2021 to determine likelihood of re-infection. In this cohort study, 2.4% developed re-infection, including two patients who had been adequately vaccinated. Two recipients who eventually were reinfected were evaluated prior to re-infection for level of immunity, which demonstrated reactive IgG testing and virus specific CD4 T cell response.

Alberici, F., et al. (2022). SARS-CoV-2 infection in dialysis and kidney transplant patients: immunological and serological response. *Journal of Nephrology*, 1–15. Retrieved from: <https://doi.org/10.1007/s40620-021-01214-8>

- Prospective, single-center case-control study assessed COVID-19 immune response in 17 ESRD patients on hemodialysis and 15 kidney transplant recipients as well as matched controls without COVID-19 between March 18 - May 22, 2020. The COVID-19 cohort showed lower numbers of CD4 + and CD8 + T cells, Natural Killer Cells, and B cells, yet the proportion of terminally differentiated B-cells was increased. Kidney transplant recipients showed lower levels of anti-spike antibodies compared to dialysis patients up to 60 days from symptom onset.

Phadke, V. K., et al. (2021). Immune responses to SARS-CoV-2 in solid organ transplant recipients. *Current Transplantation Reports*; 1–13. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7931983/>

- In studies that have compared SOT recipients with carefully matched non-transplant cohorts, levels of inflammatory markers and IL-6 are similar among hospitalized patients. As in the non-transplant population, the levels of these inflammatory markers—specifically IL-6—correlated with disease severity in some studies but are imperfect predictors of disease progression. CD4+ and CD8+ lymphopenia is more profound in SOT recipients. Additional studies are needed to understand nuances between organ types of level of immunosuppression to meaningfully inform individualized therapeutic decisions.

Hartzell, S., et al. (2020). Evidence of potent humoral immune activity in COVID-19-infected kidney transplant recipients. *American Journal of Transplantation*, 20(11), 3149–3161. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7436882/>

- Immunosuppressed kidney transplant recipients admitted to the hospital with acute COVID-19 infection can mount SARS-CoV-2-reactive adaptive immune responses. Empiric reductions in immunosuppressive therapy for all kidney transplant recipients with active COVID-19 may not be required.

15.3 Immunosuppression Management

Karruli, A., et al (2021). Effect of immunosuppression maintenance in solid organ transplant recipients with COVID-19: Systematic review and meta-analysis. *Transpl Infect Dis*, 23(4). Retrieved from: <https://doi.org/10.1111/tid.13595>

- Systematic review and meta-analysis including 202 solid organ transplant recipients evaluating maintenance immunosuppression strategies in the setting of COVID-19 disease.

Daoud, A., et al (2021). Immunosuppression in kidney transplant recipients with COVID-19 infection—where do we stand and where are we heading? *Renal Failure*; 43(1);273-80. Retrieved from: <https://doi.org/10.1080/0886022X.2021.1876730>

- Review of maintenance immunosuppression strategies in the setting of COVID-19 infection in kidney transplant recipients.

15.3.1 CNI

Salerno, D., et al. (2021). SARS-CoV-2 infection increases tacrolimus concentrations in solid-organ transplant recipients. *Clinical Transplantation*, 35(3), e14193. Retrieved from: <https://doi.org/10.1111/ctr.14193>

- A significant number of patients infected with COVID-19 infection could be overexposed to tacrolimus. Possible mechanisms include increased bioavailability in patients with anorexia, and

increased expression of IL-6 leading to decreased CYP3A4 activity. Mortality was higher in patients presenting with trough > 15 ng/mL (28.6% vs 9.9%). Closer monitoring of trough tacrolimus concentration should be considered in all SARS-CoV-2-positive solid-organ transplant patients to ensure safe drug exposure and minimize complications of immunosuppression.

Xia, T., Wang, Y. (2020). Coronavirus disease 2019 and transplantation: The combination of lopinavir/ritonavir and hydroxychloroquine is responsible for excessive tacrolimus trough level and unfavorable outcome. *Am J Transplant*;20:2630–2631. doi: 10.1111/ajt.15992. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273014/>

- The concentration of tacrolimus may increase and last for a long time after the introduction of LPV/r, even if LPV/r is discontinued promptly. Combination of immunosuppressants and LPV/r or HCQ is unfavorable for the disease improvement and protection of allograft due to over-immunosuppression, even resulting in severe cardiac toxicity due to their synergistic effect. The simultaneous use of LPV/r and HCQ in SOT recipients with COVID-19 is not recommended.

15.3.2 Antimetabolite

Chen, D., et al. (2020). Withdrawing mycophenolate mofetil in treating a young kidney transplant recipient with COVID-19: A case report. *Medicine*, 99(24), e20481. Retrieved from: <https://doi.org/10.1097/MD.00000000000020481>

- Case report of a COVID-19 infection after kidney transplantation treated with MMF withdrawal, unchanged dose of tacrolimus and oral corticosteroids, antibiotics, interferon α -2b inhalation, and traditional Chinese medicine. In certain groups of COVID-19 (e.g., mild to moderate cases, young patients without comorbidities), a reduction instead of an overall withdrawal of immunosuppressant is feasible.

15.3.3 mTORi

Granata, S., et al. (2021). mTOR-inhibition and COVID-19 in kidney transplant recipients: Focus on pulmonary fibrosis. *Frontiers in Pharmacology*, 12, 710543. Retrieved from: <https://doi.org/10.3389/fphar.2021.710543>

- A review of the current literature regarding the therapeutic potential of mTORi in kidney transplant recipients with COVID-19 with a focus on pulmonary fibrosis. The mTORi and antimetabolites have been often discontinued to minimize the risk of pulmonary toxicity and to antagonize pharmacological interaction with antiviral/anti-inflammatory drugs. However, this therapeutic strategy should be weighed against the risk of the onset of acute allograft rejections, to potentially exploit the mTORi antiviral properties, to reduce proliferation of conventional T lymphocytes (which could mitigate the cytokine storm) and to preserve Treg growth/activity which could reduce the risk of progression to severe disease.

15.3.4 Belatacept

Terrec, F., et al. (2021). Belatacept use after kidney transplantation and its effects on risk of infection and COVID-19 vaccine response. *Journal of Clinical Medicine*; 10(21), 5159. Retrieved from: <https://doi.org/10.3390/jcm10215159>

- Belatacept significantly reduces the immune response to SARS-CoV-2 mRNA vaccination. Delaying COVID-19 vaccination until 21 days after a belatacept infusion and steroid avoidance may improve immunogenicity. Several mechanisms have been proposed as belatacept plays a role at several steps in the humoral response. Most spike-specific Th cells express the co-activating molecule CD28, and could therefore become theoretically inhibited by belatacept.

COVID-19 infected belatacept-treated patients tend to require more hospitalizations, both overall and in ICUs, and mortality is greater compared to CNI-treated patients. A dedicated infection-control protocol is recommended for patients requiring belatacept.

15.3.5 Other

Zhong, Z., et al. (2020). Clinical characteristics and immunosuppressant management of coronavirus disease 2019 in solid organ transplant recipients. *Am J Transplant*;20:1916–1921. doi: 10.1111/ajt.15928. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262295/>

- Case series describing two different transplant recipients treated for COVID-19. One patient had all immunosuppression discontinued and was maintained on low-dose methylprednisolone; this patient experienced acute rejection but eventually recovered. In the second patient, tacrolimus levels were run low, along with MMF and methylprednisolone. Rejection was not seen, however the patient developed significant bone marrow suppression requiring MMF discontinuation.

15.4 Immunization

15.4.1 COVID-19 Vaccine Immunogenicity

Sanders, J.F., et al; RECOVAC Collaborators. (2022). The RECOVAC immune-response study: The immunogenicity, tolerability, and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant. *Transplantation*. doi: 10.1097/TP.0000000000003983. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34753894/>

- A prospective, controlled multicenter study of 162 participants with chronic kidney disease (CKD) stages G4/5, 159 participants on dialysis, 288 kidney transplant recipients, and 191 controls. Participants received 2 doses of the mRNA-1273 COVID-19 vaccine (Moderna). Transplant recipients had a significantly lower seroconversion rate when compared with controls (56.9% versus 100%, $P < 0.001$), with especially mycophenolic acid, but also, higher age, lower lymphocyte concentration, lower eGFR, and shorter time after transplantation being associated with nonresponder state. Transplant recipients also showed significantly lower titers of neutralizing antibodies and T-cell responses when compared with controls.

Medina-Pestana, J, et al. (2020). Inactivated Whole-virus Vaccine Triggers Low Response Against SARS-CoV-2 Infection Among Renal Transplant Patients: Prospective Phase 4 Study Results. *Transplantation*. doi: 10.1097/TP.0000000000004036. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34882589/>

- A prospective, single-center, phase 4 study of kidney transplant recipients who received two doses of CoronaVac vaccine. The proportion of patients with IgG antibodies to severe acute respiratory syndrome coronavirus 2 increased from 15.2% after first dose to 43% after second dose. Increase in antibody values after second dose was associated with higher proportion of patients with detected neutralizing antibodies. A significant reduction in the incidence of COVID-19 was observed (6.4% versus 4.2%; $P < 0.0001$), although the 28-d lethality rate remained unchanged (25% versus 22%; $P = 0.534$). CoronaVac vaccine was associated with low reactogenicity, low immunogenicity but reduced incidence of COVID-19 among kidney transplant recipients.

Gerovasili, V., et al. (2022). Impaired Humoral and Cellular Responses to SARS-CoV-2 Vaccine in Heart and Lung Transplant Recipients. *Am J Respir Crit Care Med*. doi: 10.1164/rccm.202109-2026LE. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33957273/>

- Study population consisted of 2 cohorts, SARS-CoV-2 infection naive healthcare workers (HCW) (n=69) and highly immunosuppressed cardiothoracic transplant recipients (HICTTR) (n=58). Serum was tested for antibodies to nucleocapsid protein (anti-NP) and antibodies to the Receptor

Binding Domain of Spike protein. SARS-CoV-2 specific T-cell responses were detected using the T-SPOT® Discovery SARS-CoV-2. Seroconversion was observed in 15/58 (26%) HICCTR. T cell immune responses to SARS-CoV-2 peptides were detected in 91% of HCW compared to 21% of HICTTR ($p < 0.0001$).

Liefeldt, L., et al. (2022). Predictors of Serological Response to SARS-CoV-2 Vaccination in Kidney Transplant Patients: Baseline Characteristics, Immunosuppression, and the Role of IMPDH Monitoring. *J Clin Med*. doi: 10.3390/jcm11061697. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35330022/>

- A cohort study that analyzed the determinants of vaccination response in kidney transplant recipients without history of COVID-19. In vaccine responders, the time after transplantation was longer (13.5 vs. 8.5 years), the glomerular filtration rate was higher (56.9 vs. 47.8 mL/min/1.73 m²), and responders were younger (53.0 vs. 57.4 years). Heterologous vaccination was more effective than homologous vaccination. Calcineurin inhibitors plus mycophenolate reduced the seroconversion rate. No seroconversion was observed in belatacept patients. In mycophenolate-treated patients, IMPDH activity was a significantly better predictor of response than mycophenolate dose (AUC 0.84 vs. 0.62, $p < 0.001$).

Herrera, S., et al. (2022). Cellular and humoral immune response after mRNA-1273 SARS-CoV-2 vaccine in liver and heart transplant recipients. *Am J Transplant*. doi: 10.1111/ajt.16768. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34291552/>

- A prospective of heart and liver transplant who received 2 doses of the Moderna mRNA vaccine. Median time from transplantation to vaccination was 5.4 years (IQR 0.3–27). Sixty-four percent of patients developed SARS-CoV-2 IgM/IgG antibodies and 79% S-ELISpot positivity. Ninety percent of recipients developed either humoral or cellular response (87% in heart recipients and 93% in liver recipients). Factors associated with vaccine unresponsiveness were hypogammaglobulinemia and vaccination during the first year after transplantation.

Rozen-Zvi, B., et al. (2021). Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect*. doi: 10.1016/j.cmi.2021.04.028. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33957273/>

- A prospective cohort study of kidney transplant recipients who received 2 doses of SARS-CoV-2 mRNA vaccine. Patients were tested for anti-S antibodies 2-4 weeks after receiving the second dose. Factors associated with antibody response were higher estimated glomerular filtration rate ($p < 0.001$), lower mycophenolic acid dose ($p < 0.001$), younger age ($p < 0.001$) and lower calcineurin inhibitor blood level ($p 0.014$).

Holden, I.K., et al. (2021). Immunogenicity of SARS-CoV-2 mRNA vaccine in solid organ transplant recipients. *Journal of Internal Medicine*; 10.1111/joim.13361. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8447120/>

- Protective levels of SARS-CoV-2 IgG antibodies after infection or vaccination have not yet been established. Most SOT recipients in this preliminary study had a poor response to 2 doses of the mRNA Covid-19 vaccines. SOT recipients require continuous use of personal protective measurements even after vaccination.

Boyarsky, B.J., et al. (2021). Antibody response to the Janssen COVID-19 vaccine in solid organ transplant recipients. *Transplantation*;105(8):e82-e83. doi: 10.1097/TP.0000000000003850. Retrieved from:

https://journals.lww.com/transplantjournal/Fulltext/2021/08000/Antibody_Response_to_the_Janssen_COVID_19_Vaccine.35.aspx

- At a median (IQRs) 33 d (31–44) after vaccination, anti-receptor-binding domain (RBD) antibody was detectable in only 2 of 12 participants who received the Janssen vaccine compared with 430 of 725 who completed the mRNA vaccine series (17% versus 59%, $P=0.005$). Those who received the Janssen vaccine had lower odds (OR 0.11; 95% CI, 0.02-0.53; $P=0.006$) of developing anti-RBD antibodies than those who completed the mRNA series.

15.4.2 Booster Doses

Masset, C., et al. (2022). A fourth SARS-CoV-2 mRNA vaccine in strictly seronegative kidney transplant recipients. *Kidney Int.* doi: 10.1016/j.kint.2022.01.017. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/35167873/>

- A retrospective evaluation of 49 nonresponder kidney transplant recipients with a serologic assessment following a fourth mRNA vaccine. Serologic screening was assessed in a median of 35 days following the fourth injection. A total of 21 of 49 patients (42.8%) seroconverted. Between responders and nonresponders, lower steroid use (47% vs. 64%), less lymphopenia (62% vs. 75%), longer time between the third and fourth dose (93 vs. 82 days), and a larger utilization of the BNT162b vaccine (86% vs. 68%) were noted in patients who developed a humoral response.

Feingold, B., et al. (2022). Responsiveness to second and third dose of mRNA COVID-19 vaccination in adolescent and young adult heart transplant recipients. *Pediatr Transplant.* doi: 10.1111/petr.14272.

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35340096/>

- Retrospective review of 28 vaccinated adolescent and young adult HT recipients from a single institution. At a median of 98.5 days after the second dose, 17 (61%) had an Ab response. Among 12 who had serology before and after third-dose vaccination, four of seven who were negative prior to the third dose became positive at a median of 34 days following the third dose. No myocarditis, acute rejection, graft dysfunction, graft loss, or deaths were observed.

Odrizola, A., et al. Immune Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Liver Transplant Recipients. *Transplantation.* doi: 10.1097/TP.0000000000004147. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/35323163/>

- Review of the antibody responses induced to 2 dose vaccination and a subsequent third dose of the mRNA-1273 SARS-CoV-2 vaccine in 129 LTRs. After 2 dose vaccination, seronegative, low, and high responses were observed in 16 (12.4%), 51 (39.6%), and 62 (48%) patients, respectively, whereas, after third dose, the frequency of seronegatives, low, and high responders was 4 (3.1%), 8 (6.2%), and 117 (90.7%) patients, respectively. Twelve of 16 seronegative LTRs after 2 doses produced weak antibody response after the third dose. Nonresponse after third dose was associated with mofetil mycophenolate treatment (75% versus 23.2%) ($P<0.001$), a higher dose of this drug (1666 [SD, ± 577] versus 1068 [SD, ± 394] mg) ($P=0.02$), and lower estimated glomerular filtration rate (32.3 [SD, ± 17.3] versus 69.4 [SD, ± 18.9] mL/min/1.73m²) ($P=0.001$). The overall immune response detected after third dose was 126 of 129 (97.67%). Our findings suggest that the third dose induces a more robust antibody response according to a protective immunity in LTRs, in agreement with data in other SOTRs.

Havlin, J., et al. (2021). Impaired humoral response to third dose of BNT162b2 mRNA COVID-19 vaccine despite detectable spike protein-specific T cells in lung transplant recipients, *Transplantation.* Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/34856599/>

- In the absence of humoral response, emergence of cellular response was detected in 47% of lung transplant recipients after the third vaccine dose, which might have a clinical benefit; however, the measurable response is low, dominantly cellular, and only detectable in half of the patients.

Abedon, A.T., et al. (2022). Improved Antibody Response After a Fifth Dose of a SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Transplantation*. doi: 10.1097/TP.0000000000004092. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35175241/>

- A case series of 18 SOTRs who received a 5th dose of a SARS-CoV-2 vaccine. There were 8 (44%) kidney, 4 (22%) liver, 3 (17%) lung, 2 (11%) heart, and 1 (6%) liver-kidney recipients. Pre-D5, 2 of 18 (11%) SOTRs were seronegative. Of 12 SOTRs on MMF, 4 of 12 (33%) modified their MMF dose surrounding D5: 2 discontinued MMF (1 temporarily) and 2 reduced their doses (25% and 50%, respectively) before receiving D5. 17 of 17 patients (100%) who tested on the same platform had higher antibody titers, whereas 1 tested seronegative on 2 different platforms before and after D5. There were no self-reported episodes of rejection or COVID-19 infection. D5 side effects were minimal and consistent with previous findings.

Reindl-Schwaighofer, R., et al. Comparison of SARS-CoV-2 Antibody Response 4 Weeks After Homologous vs Heterologous Third Vaccine Dose in Kidney Transplant Recipients: A Randomized Clinical Trial. *JAMA Intern Med*. doi: 10.1001/jamainternmed.2021.7372. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34928302/>

- A single center, randomized clinical trial of a third dose of vaccine against SARS-CoV-2, in 201 KTRs who had not developed SARS-CoV-2 spike protein antibodies after 2 doses of an mRNA vaccine. Patients were given mRNA (BNT162b2 or mRNA-1273) or vector (Ad26COVS1) as a third dose of a SARS-CoV-2 vaccine. 39% developed SARS-CoV-2 antibodies after the third vaccine. There was no statistically significant difference between groups, with an antibody response rate of 35% and 42% for the mRNA and vector vaccines, respectively. Only 22% of seroconverted patients had neutralizing antibodies. Similarly, T-cell response was low with only 17 patients showing a positive response after the third vaccination. Receiving nontriple immunosuppression, longer time after kidney transplant, and torque teno virus plasma levels were associated with vaccine response. The third dose of an mRNA vaccine was associated with a higher frequency of local pain at the injection site compared with the vector vaccine, while systemic symptoms were comparable between groups.

Peled, Y., et al. (2022). Third dose of the BNT162b2 vaccine in heart transplant recipients: Immunogenicity and clinical experience. *The Journal of Heart and Lung Transplantation*, 41(2), 148–157. Retrieved from: <https://doi.org/10.1016/j.healun.2021.08.010>

- A third dose of the Pfizer BioNTech mRNA vaccine given to 96 adult HT patients was associated with a low rate of adverse events, and no episodes of rejection. At 18 days following the third dose of the vaccine, the positive antibody response increased from 23% to 67%, with a corresponding increase in neutralizing capacity. The third dose elicited SARS-CoV-2 neutralization titers >9-fold and IgG anti-RBD antibodies >3-fold of the range achieved after the two primary doses. Mycophenolate use, lower eGFR and higher C-reactive protein were associated with a reduced likelihood of generating an immune response. A specific T-cell response following the third dose was evident in the majority of transplant recipients.

Kamar, N., et al. (2021). Assessment of 4 doses of SARS-CoV-2 messenger RNA-based vaccine in recipients of a solid organ transplant. *JAMA network open*, 4(11), e2136030. Retrieved from: <https://doi.org/10.1001/jamanetworkopen.2021.36030>

- Case series of 37 patients who received 4th dose of Pfizer-BioNTech mRNA vaccine. Anti-SARS-CoV-2 antibodies detected in 5 patients (13.5%) before dose 4 and in 18 patients (48.6%) 1 month later ($p = .002$). At 4 weeks after dose 4, antibody concentrations were significantly higher among patients who had detectable antibodies before dose 4 than among those who had no

response. However, neutralizing antibody titers at 4 weeks after dose 4 did not differ between responders and non-responders to 3 doses. No serious adverse event or acute rejection observed after dose 4.

Hall, V.G., et al. (2021). Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. *N Engl J Med*;385:1244-1246. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8385563/>

- A third dose of the mRNA-1273 vaccine (Moderna) in transplant recipients had substantially higher immunogenicity compared to placebo when administered 2 months after the second dose of mRNA-1273, as evidenced by improved anti-receptor-domain binding (RDB) antibody level, percent virus neutralization and polyfunctional T cell response.

Kamar, N., et al. (2021). Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med*;385:661-662. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8262620/>

- Study of 101 consecutive solid-organ transplant recipients (mean [\pm SD] age, 58 \pm 2 years; 69% were men) who were given three doses of the messenger RNA vaccine BNT162b2 (Pfizer–BioNTech). The first two doses were given 1 month apart, and the third dose was administered 61 \pm 1 days after the second dose. The time between transplantation and the initiation of vaccination was 97 \pm 8 months. The prevalence of anti–SARS-CoV-2 antibodies was 0% (95% confidence interval [CI], 0 to 4; 0 of 101 patients) before the first dose, 4% (95% CI, 1 to 10; 4 of 101 patients) before the second dose, 40% (95% CI, 31 to 51; 40 of 99 patients) before the third dose, and 68% (95% CI, 58 to 77; 67 of 99 patients) 4 weeks after the third dose. Administration of a third dose of the BNT162b2 vaccine to solid-organ transplant recipients significantly improved the immunogenicity of the vaccine, with no cases of Covid-19 reported in any of the patients.

15.4.3 Breakthrough Infections/Vaccine Failure

Rodríguez-Espinosa, D., et al. (2022). Incidence of severe breakthrough SARS-CoV-2 infections in vaccinated kidney transplant and haemodialysis patients. *J Nephrol*. doi: 10.1007/s40620-022-01257-5. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35191008/>

- Observational prospective study of kidney transplant recipients and hemodialysis patients vaccinated with 2 doses of Pfizer or Moderna mRNA vaccine. Among patients on hemodialysis, 6% (18/302) infected with COVID-19, of whom four required hospital admission (1.3%), only one (0.3%) had severe COVID-19, and none of them died. Among kidney transplant recipients, 4.3% (44/1034) of KTRs were infected, and presented more hospital admissions (26 patients, 2.5%), severe COVID-19 (11 patients, 1.1%) or death (4 patients, 0.4%). Kidney transplant recipients had a significantly higher risk of hospital admission than patients on hemodialysis, and this risk increased with age and male sex (HR 3.37 and 4.74, respectively). The study highlights the need for booster doses in kidney transplant recipients.

Ali, N. M., et al (2021). Development of COVID-19 infection in transplant recipients after SARS-CoV-2 vaccination. *Transplantation*, 105(9), e104–e106. Retrieved from: <https://doi.org/10.1097/TP.0000000000003836>

- A retrospective chart review of 14 solid organ transplant (SOT) recipients (10 kidney, 2 liver, 1 lung, and 1 heart) with a median age of 62 (27–78) y who were diagnosed with COVID-19, a median of 23.5 (3–57) d after completion of SARS-CoV-2 vaccination (8 Pfizer, 5 Moderna, 1 JNJ). Seven (50%) patients were hospitalized, 5 with severe COVID-19. All patients with severe disease received dexamethasone and remdesivir; 2 patients also received interleukin-6 inhibitor and 2 received convalescent plasma. Seven (50%) patients were treated with monoclonal

antibody infusion outside of the hospital; however, 2 of these patients required admission for progressive illness. Two patients remained hospitalized, 1 died, and 11 recovered at home.

15.4.4 Impact of Immunosuppression on Immunization Response

Schrezenmeier, E., et al. (2022). Temporary antimetabolite treatment hold boosts SARS-CoV-2 vaccination-specific humoral and cellular immunity in kidney transplant recipients. JCI insight, e157836. Retrieved from: <https://doi.org/10.1172/jci.insight.157836>

- Prospective observational study of 29 low-immunological risk kidney transplant recipients receiving their 4th dose of vaccine after failing to mount a humoral immune response to prior SARS-CoV-2 vaccines. Antimetabolite was held for 5 weeks around the time of the 4th vaccine, starting 4-7 days prior to vaccination (MPA in 28 patients, AZA in 1 patient). Seroconversion of anti-S1 domain IgG above the threshold for positivity was observed on day 32 in 76% (22/29) of patients.

Meunier, L., et al. (2022). Mycophenolate mofetil decreases humoral responses to three doses of SARS-CoV-2 vaccine in liver transplant recipients. Liver International, 10.1111/liv.15258. Retrieved from: <https://doi.org/10.1111/liv.15258>

- Multicenter, retrospective observational study of 327 adult liver transplant recipients examining humoral response to SARS-CoV-2 vaccination. Patients received one (n=16), two (n=63), or three vaccine doses (n=248). Optimal serologic response was met in 172 patients (52.6%). Mycophenolate mofetil (MMF) use was an independent risk factor for vaccination response failure (p=0.008).

Mitchell, J., et al. (2022). Humoral and cellular immune response to a third dose of SARS-CoV-2 vaccine in kidney transplant recipients taking belatacept. Transplantation, 10.1097/TP.0000000000004100. Retrieved from: <https://doi.org/10.1097/TP.0000000000004100>

- Letter to the Editor evaluating vaccination response in 25 kidney transplant recipients on belatacept and 26 kidney transplant control subjects who received 3 doses of SARS-CoV-2 vaccine. Antispikeserological testing was performed 1 month after the 2nd dose and 2-4 weeks after the 3rd dose. The belatacept group had lower antispikeseroconversion compared to the control group after the 3rd dose (p=0.003).

Mitchell, J., et al. (2022). Effect of mycophenolate mofetil dosing on antibody response to SARS-CoV-2 vaccination in heart and lung transplant recipients. Transplantation, 10.1097/TP.0000000000004090. Retrieved from: <https://doi.org/10.1097/TP.0000000000004090>

- Letter to the Editor assessing the effect of cumulative daily dose of mycophenolate mofetil (MMF) on antispikeserological antibody titers after 2 doses of SARS-CoV2 mRNA vaccine in heart and lung transplant recipients. Antispikeserological antibody testing was performed at 1, 3 and 6 months after the 2nd vaccine dose in 212 patients without a previously confirmed COVID-19 diagnosis. Patients on less than 1000 mg/day had a similar risk of vaccine nonresponse compared to a cohort not on MMF (p=0.63). Those on doses of 1000 mg/day or greater had >2 fold higher risk of vaccine response failure (p<0.01).

Joerns, J., et al. (2022). High-dose mycophenolate use at vaccination is independently associated with breakthrough COVID-19 among lung transplant patients. Transplantation. doi: 10.1097/TP.0000000000004089. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35250007/>

- A cohort of lung transplant recipients who had been vaccinated against COVID-19 (2 doses of Pfizer or Moderna mRNA vaccine) and experienced a breakthrough infection was compared to a control group of lung transplant recipients who had been vaccinated against COVID-19 without

infection. All patients were maintained on standard triple IS per protocol at the time of vaccination. The median time from vaccination to breakthrough infection was 138 d (range, 42–179 d). Patients with breakthrough infection seemed more likely to be on MMF as the antimetabolite ($P=0.15$), and a higher proportion of patients with breakthrough infection were on daily MMF dose of $>1000\text{mg}$ ($P=0.03$).

Abravanel, F., et al. (2022). Humoral and cellular immune responses of solid organ transplant patients on belatacept to three doses of mRNA-based anti-SARS-CoV-2 vaccine. *Vaccines*, 10(3), 354. Retrieved from: <https://doi.org/10.3390/vaccines10030354>

- The humoral response to 3 doses of the BNT162b2 mRNA COVID-19 vaccine (BioNTech, Pfizer) in belatacept-treated solid organ transplant patients (62 kidney transplant and 6 heart transplant recipients) was analyzed. At 1 month after the 2nd dose of vaccine, anti-spike antibodies were detectable in 5/68 (7.4%) patients and at 1 month after the 3rd dose this increased to 16/68 (23.5%). Only 7 patients (10%) developed antibody titers greater than 141 BAU/mL which provides 89.3% protection in immunocompetent patients. The T-cell responses were also assessed in a subgroup of 17 patients, and it was found these correlated well with the humoral response. Patients on tacrolimus plus belatacept were more likely to produce a lower immune response.

Kantauskaite, M., et al. (2022). Intensity of mycophenolate mofetil treatment is associated with an impaired immune response to SARS-CoV-2 vaccination in kidney transplant recipients. *American Journal of Transplantation*, 22(2), 634–639. Retrieved from: <https://doi.org/10.1111/ajt.16851>

- Multicenter, prospective observational study examining post-vaccination IgG antibodies against SARS-CoV-2 spike S1 subunit and neutralization capacity in 225 kidney transplant recipients and 176 control subjects. After vaccination, 56 (24.9%) of kidney transplant recipients became seropositive and 68% had neutralizing antibodies, which was significantly lower compared to the control group ($p < 0.0001$). It was found that mycophenolate mofetil was the strongest predictor of impaired vaccination response and a multivariate regression analysis showed that a MMF-free regimen was highly associated with seroconversion ($p < 0.001$). Patients on MMF developed antibodies 13.9% of the time and 23/26 of those that developed antibodies while on MMF were on doses of 1gm/day or less demonstrating potential for a dose-dependent unfavorable effect.

Netti, G. S., et al. (2022). mTOR inhibitors improve both humoral and cellular response to SARS-CoV-2 messenger RNA BNT16b2 vaccine in kidney transplant recipients. *American Journal of Transplantation*, 10.1111/ajt.16958. Retrieved from: <https://doi.org/10.1111/ajt.16958>

- Multicenter, observational, case-control study with 132 kidney transplant recipients comparing response to the SARS-CoV-2 mRNA BNT16b2 vaccine (BioNTech, Pfizer) in patients who received maintenance immunosuppression with either tacrolimus, mycophenolate mofetil and prednisone or tacrolimus, everolimus and prednisone. Patients treated with everolimus showed a significantly higher anti-SARS-CoV-2 IgG titer ($p=0.003$) compared to the mycophenolate cohort. SARS-CoV-2-specific T-cell-derived IFN γ release was also significantly increased in patients on everolimus ($p < 0.001$).

15.5 Treatment

15.5.1 Antiviral Therapy

Elec, F., et al. (2022). COVID-19 and kidney transplantation: the impact of remdesivir on renal function and outcome - a retrospective cohort study. *Int J Infect Dis*. doi: 10.1016/j.ijid.2022.03.015. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35301103/>

- Study of 165 renal transplant recipients hospitalized due to COVID-19. 38 patients received a 5-day course of remdesivir (RDV), while 127 patients received standard of care (SOC). RDV treatment was completed in all patients without any adverse effects attributable to RDV. There was no difference in overall mortality between the RDV and SOC groups (18% vs 23%, $p > 0.05$), but the ICU mortality was significantly reduced in the RDV group (39% vs 83%, $p < 0.05$). RDV appeared to have no nephrotoxic effect on renal transplant recipients as there was no difference in the incidence of AKI between RDV and SOC groups (50% vs 43%, $p > 0.05$), and the discharge eGFR values significantly improved in the RDV group compared with the admission values. Five-day RDV treatment appears safe in KTx recipients, and without obvious nephrotoxic effects. Also, RDV may decrease ICU mortality attributed to COVID-19.

Salerno, D.M., et al. (2022). Early clinical experience with nirmatrelvir/ritonavir for the treatment of COVID-19 in solid organ transplant recipients. *Am J Transplant*. doi: 10.1111/ajt.17027. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35278260/>

- A retrospective study of 25 adult solid organ transplant recipients on a calcineurin inhibitor or mammalian target of rapamycin inhibitor ($n = 21$ tacrolimus, $n = 4$ cyclosporine, $n = 3$ everolimus, $n = 1$ sirolimus). All patients were instructed to follow the following standardized protocol during treatment with 5 days of nirmatrelvir/ritonavir (NR): hold tacrolimus or mTOR inhibitor or reduce cyclosporine dose to 20% of baseline daily dose. Median tacrolimus level pre- and post-NR were 7.4 ng/ml (IQR, 6.6-8.6) and 5.2 (IQR, 3.6-8.7), respectively. Four patients experienced a supratherapeutic tacrolimus concentration after restarting tacrolimus post-NR. The clinically significant interaction between NR and immunosuppressive agents can be reasonably managed with a standardized dosing protocol.

Raja, M.A., et al (2021). COVID-19 in solid organ transplant recipients: A systematic review and meta-analysis of current literature. *Transplant Rev*, 35(1). Retrieved from: <https://doi.org/10.1016/j.trre.2020.100588>

- Systematic review including 215 studies and 2772 solid organ transplant recipients (and meta-analysis including 60 studies) evaluating treatment strategies and outcomes related to SARS-CoV-2 infection.

Laracy, J.C., et al. (2020). Antivirals for COVID-19 in solid organ transplant recipients. *Current Transplantation Reports*. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7575337/>

- There are no trials investigating antiviral agents primarily in SOT recipients and the major studies published so far have included few patients with any form of immunosuppression, especially SOT recipients. Therefore, the clinical impact of remdesivir and other therapies can only be extrapolated from these non-transplant patient populations. The overall approach to antiviral therapy for COVID-19 in SOT recipients should be similar to the general population and that the general recommendations in the NIH and IDSA COVID-19 guidelines should be applied to these patients as well.

15.5.2 Immunomodulatory Therapy

Pinchera, B., et al; Federico II COVID team. (2022). Sotrovimab in solid organ transplant patients with early, mild/moderate SARS-CoV-2 infection: A single-center experience. *Transplantation*. doi: 10.1097/TP.0000000000004150. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35349534/>

- A case series of 15 SOT recipients who received sotrovimab. Thirteen patients (86%) had received mRNA COVID-19 vaccines. At the time of infusion, 13 (87%) patients had a mild disease, 2 (13%) a moderate disease, and none showed a severe COVID-19. No allergic reaction

or other adverse events were reported during the infusion or in the next 4 weeks. Two patients (13%) needed hospitalization (after 1 and 3 days) because of rapidly progressive respiratory distress requiring oxygen supplementation. No patients died. At day 28, 10 patients (66.7%) achieved virologic clearance.

Del Bello, A., et al. (2021). Anti-SARS-CoV-2 monoclonal antibodies in solid-organ transplant patients. Transplantation. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8487703/>

- Study of 16 SOT patients in France who received monoclonal antibodies compared with a control group of 36 patients who did not. Five patients were given bamlanivimab monotherapy (700 mg), 9 patients received the combination treatment (700 mg of bamlanivimab and 1400mg of etesevimab), and 2 patients have received the combination of casirivimab and imdevimab (1200mg/1200mg). After a follow-up of 39 (10-74) days after the injection of monoclonal antibodies, none of these 16 patients developed a severe respiratory illness defined by the need for high oxygen support, while 15 out the 32 control patients developed a severe respiratory illness (46.9%, $p=0.007$), requiring high flow nasal oxygen ($n=7$) or orotracheal intubation ($n=8$).

15.6 Organ Donation during COVID-19 Pandemic

Strauss, A.T., et al. (2020). Liver transplantation in the United States during the COVID-19 pandemic: national and center-level responses. Am J Transplant. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33107180/>

- From March 15 to April 30 2020, there was no change in new listings or DDLT in states with the lowest COVID-19 burden, but in states with the highest incidence, there were 33% fewer new listings than expected and 34% fewer DDLTs. The changes in DDLT occurred differently across MELD scores; there were 35.4% fewer DDLTs than expected for MELD 15-19 and 50.4% more DDLT than expected for MELD 30-34. Early in the pandemic, LDLTs were 65% fewer than expected in states with the highest burden. In the states with the highest COVID-19 incidence early in the pandemic, there was a 59% increase in deaths on the waitlist observed compared to expected.

Kumar, D., et al (2020). COVID-19: A global transplant perspective on successfully navigating a pandemic. Am J Transplant. 2020 March 23. <https://www.ncbi.nlm.nih.gov/pubmed/32202064>

- A summarization of collective viewpoints on the emerging COVID-19 pandemic, including mitigation strategies and impact on organ transplantation.

15.7 COVID- 19 Positive Donors

Ibrahim, M.M., et al. (2022). Kidney transplantation from COVID-19 deceased donors: new hope on the horizon. Am J Nephrol. doi: 10.1159/000522597. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35344961/>

- Two cases of kidney transplantation from a COVID-19-positive deceased donor into recipients who had negative SARS-CoV-2 nasopharyngeal swab PCRs prior to transplantation. Patients received induction with antithymocyte globulin and had appropriate renal graft function. Both recipients demonstrated no signs or symptoms of COVID-19 infection within 16 weeks of transplant. These 2 cases may broaden the scope of accepting organs from COVID-19-positive deceased donors.

Jayasekera, C.R., et al. (2022) Solid organ transplantation from SARS-CoV-2-infected donors to uninfected recipients: A single-center experience. Transplant Direct. doi: 10.1097/TXD.0000000000001286. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35047665/>

- A single center transplanted 2 livers, 1 simultaneous liver and kidney, 1 kidney and 1 simultaneous kidney and pancreas from SARS-CoV-2-infected donors into 5 uninfected

recipients. None of the recipients developed SARS-CoV-2 or COVID-19 and allograft biopsies did not show evidence of SARS-CoV-2 RNA. Transplanting nonthoracic organs from SARS-CoV-2-infected into uninfected recipients demonstrated no evidence of virus transmission.

Kates, O.S., et al. (2020). Use of SARS-CoV-2-infected deceased organ donors: Should we always “just say no?” *Am J Transplant*; 20:1787–1794. doi: 10.1111/ajt.16000. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7272824/>

- The possibility of donor to recipient transmission of SARS-CoV-2 cannot be excluded with the existing clinical data, but, for some patients, that uncertainty may be preferable to the alternative. A critical review of available data and biology of SARS-CoV-2 and related RNA respiratory viruses suggests that the risk for transplant transmission is low, especially among donors with mildly symptomatic or asymptomatic infection. For selected patients with high waitlist mortality, transplant programs should consider accepting heart or liver transplants from deceased donors with SARS-CoV-2 infection.