

Preventing Coronavirus Disease 2019 in Kidney Transplant Recipients: Where Should We Begin?

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A comment on "Willicombe et al.: Identification of patient characteristics associated with SARS-CoV-2 infection and outcome in kidney transplant patients using serological screening. *Transplantation*. 2021 Jan 1;105(1):151–7."

Keywords

Acute rejection · Immunology · Renal transplantation · SARS-CoV2 · Vaccine

Abstract

Context: Chronic immunosuppression is associated with an increased risk of opportunistic infections. Although kidney transplant recipients with coronavirus disease 2019 (COVID-19) have higher mortality than the general population, data on their risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are unknown. **Subject of Review:** A recent single-center screening study from the UK (*Transplantation*. 2021 Jan 1;105(1):151–7) showed that 89 (10.4%) of 855 consecutive kidney transplant recipients tested positive for SARS-CoV-2 antibodies. Risk factors for infection included a nonwhite background, diabetes, and a history of allograft rejection. Risk factors for mortality in in-

dividuals who developed COVID-19 were older age and receiving steroids. **Second Opinion:** This study shows that the rate of SARS-CoV-2 infection in kidney transplant recipients is similar to the one observed in the general population in the same area (13%), indicating that transplant recipients are not at increased risk of COVID-19. However, the investigators raise the interesting point that since transplant individuals were advised to shelter earlier than the general population, they may be in fact more susceptible. This statement is hard to substantiate, but the identification of specific risk factors for infection and poor outcomes is crucial to tailor strategies to prevent spread of the infection. This is particularly important, considering that kidney transplant recipients may be at increased risk of prolonged viral spread and in-host viral mutations, making them not just a particularly fragile population for COVID-19 but also a potentially major source of further contagions.

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Kidney Transplant Recipients and SARS-CoV-2 Infection

Immunosuppression is a major risk factor for opportunistic infections [1]. Therefore, since the very beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, kidney transplant recipients have been considered a fragile population at higher risk of infection and poor outcomes [2, 3]. Finding that the most common risk factors for mortality in coronavirus disease 2019 (COVID-19), such as older age, diabetes, and hypertension, are also common in transplanted individuals further supported this notion.

Initial series of hospitalized kidney transplant recipients with COVID-19 showed alarming rates of mortality, between 25 and 35% [4]. These rates are higher than in-hospital case-fatality rates reported in the general population (ranging between 10 and 20%) [5–7]. However, there are also series showing that solid organ recipients have similar COVID-19-related mortality rates than the general population [8]. This suggests that such increased risk might be mitigated, for instance, by early hospitalization and a greater ease of access to intensive care unit [8].

Progressive failure of most initially tested therapeutic approaches for COVID-19 further alarmed the transplant community that was progressively left without real therapeutic options. Effective prevention of COVID-19 infection in kidney transplant recipients, a population in need for frequent monitoring of graft function with blood draws, and often complex therapies has been therefore a challenging effort [9]. General measures for infectious disease prevention do apply to transplant patients, similar to the general population. However, identification of specific risk factors for infection may allow to strengthen rigor in selected patients, while avoiding excessive precautions in others, overall permitting a safe working and social activity.

In this context, we welcome the large serological screening by Willicombe et al. [10] providing new, important data on risk factors for SARS-CoV-2 infection in kidney transplant recipients. This study measured anti-SARS-CoV-2 antibody levels in 855 consecutive kidney transplant recipients out of a cohort of 1,250 patients followed at Imperial College Renal and Transplant Center, London, UK. Eighty-nine (10.4%) patients tested positive for SARS-CoV-2 antibodies. For comparison, the seroprevalence in London around the same period was 13%. This supports the concept that kidney transplant recipients are at similar risk for SARS-CoV-2 infection compared to the general population. Considering that trans-

plant recipients were advised to shield in the UK months earlier than the general population and their generally more cautious attitude to limit exposure to infections, the authors of the study predicted a much lower exposure rate. However, the fact that family members may not always be as careful as the transplant recipients makes this conclusion hard to substantiate.

How Should We Define SARS-CoV-2 Infection in Transplant Recipients?

Ideally, viral PCR screening would be required to assess asymptomatic cases of infection. However, this approach is extremely demanding and would require serial tests to capture the infection in patients without symptoms. Antiviral antibody measurement seems therefore the most effective approach as antibodies are thought to persist in the circulation for months after the infection, even in the asymptomatic cases. However, antibody screening has its own limitations as it may underestimate the prevalence of individuals who experienced viral infection. In particular, kidney transplant recipients may not develop an effective antibody response, or anti-SARS-CoV-2 antibodies may disappear weeks after infection. In this study, only 10% of patients with positive RT-PCR results did not have detectable antibodies at 1 month after infection, but this number could increase in patients with asymptomatic disease or at later time points after infection. Therefore, the infection risk of transplant recipients may in fact be significantly higher than the one reported here.

The same UK group recently published in a separate article the comparisons between different anti-SARS-CoV-2 antibody assays in supposedly the same cohort of patients [11]. They performed a comparison between 3 serological assays and found that the 2 immunoassays that tested for the presence of antibodies against the RBD of the S protein were superior to the one they used for the detection of antibodies reactive for the NP antigen.

What Are the Risk Factors for SARS-CoV-2 Infection in Transplant Recipients?

In the UK study, risk factors for the development of anti-SARS-CoV-2 antibodies included a nonwhite background, a diagnosis of diabetes, and a history of allograft rejection. The association between ethnicity and diabetes with COVID-19 infection is consistent with risk factors

for COVID-19 found in studies within the general population [12, 13] and with prior studies identifying common risk factors for posttransplant infections [14].

Less clear is the association between acute rejection and increased infection risk, which could be related in part to the greater cumulative exposure to immunosuppressive drugs after rejection. It is also possible that rejection episodes were a sign of poor adherence to immunosuppressive therapy and, possibly, worse compliance to recommended medical preventive strategies against the virus. The authors also emphasize that patients enrolled in this single-center study [10] received steroids only if they had prior rejection episodes or if they were using steroids before transplantation. Therefore, the rejection-associated risk could be driven by the use of steroids due to a prior episode, similar to the results of studies in other immunosuppressed populations, suggesting that glucocorticoid exposure increases the risk of severe COVID-19 disease [15]. In this respect, it will be important to identify specific risk factors for steroid toxicity that put people at risk for SARS-CoV-2 infection. With the limitations of a single-center, cross-sectional study, this report provides important information in the identification of kidney transplant patients in whom preventive strategies should be reinforced the most.

Is the Antiviral Immune Response Impaired in Transplanted Individuals?

While high rates of infections and poor outcomes in transplant patients suggest an impaired immune response, the few available immune phenotypic analyses [16] and anti-SARS-CoV-2 antibody measurements in infected individuals did not detect major abnormalities. However, anti-SARS-CoV-2 T-cell responses in transplanted patients have not been investigated extensively.

The anti-SARS-CoV-2 antibodies measured in the UK study were targeted against the RBD viral antigen [10]. There is evidence that anti-RBD antibodies may provide information on functional immunity, given reported correlations between RBD antibodies and neutralizing antibodies [17, 18]. However, ad hoc functional studies testing the viral-neutralizing capacity of the anti-SARS-CoV-2 antibodies produced by transplant recipients are needed. Understanding the antiviral response in kidney transplant recipients is key not just to interpret data of antibody screening studies but more importantly to manage immunosuppression during COVID-19 and for future vaccine strategies.

Should We Isolate Infected Transplant Recipients Longer Than Non-Immunosuppressed Individuals?

An immunosuppressive state may associate with higher risk of persistent infections and viral spread than people from the general population. It may also be associated with higher viral shedding. Recently, the cases of immunocompromised individuals with persistent (over 5 months) viral infection have been reported [5, 19]. Importantly, ex vivo studies suggest that the virus that is persistently shed by immunosuppressed individuals would still be able to establish productive infection in contacts upon transmission [19]. If confirmed also in transplanted individuals, this may suggest that longer quarantine periods and repeated negative tests may be needed for transplant recipients who recover from COVID-19. In particular, monitoring of genomic and subgenomic RNA might be required to exclude persistence of SARS-CoV-2 infection [19].

Importantly, an immunocompromised state has been shown to accelerate in-host SARS-CoV-2 viral evolution and formation of new viral variants [5, 19]. Potential factors contributing to the observed within-host evolution is prolonged infection and the compromised immune status of the host, possibly resulting in a different set of selective pressures compared with an immune-competent host. This could be particularly important based on recent data suggesting that a more sustained antibody response and greater CD4+ T-cell activation with increased somatic mutations on B cells are associated with shorter disease trajectories [20]. Mutations that alter RNA virus may affect SARS-CoV-2 virulence and transmissibility and facilitate global spread, similar to what happened with D614G mutation [21].

Preventing SARS-CoV-2 Infection in Transplant Recipients and How This Pandemic Has Changed Transplant Medicine

The ultimate strategy to effectively prevent COVID-19 is vaccination against SARS-CoV-2. Recently approved vaccines, including mRNA-based vaccines, have shown great promise in terms of safety/efficacy profile [22, 23]. Luckily, anti-SARS-CoV-2 vaccines are already being distributed worldwide, and transplant recipients have initiated vaccination in multiple locations with major variability in timing driven by government policies and availability of vaccines. Although data in transplant patients are limited, it is reasonable to think, based on data with

other vaccines [24], that their immune responses will be protective, although the degree of protection and its duration are still unknown.

Strategies to prevent infection in transplant recipients are still important while vaccine is being delivered, in particular the use of masks and avoidance of crowded non-ventilated spaces. The COVID-19 outbreak has seriously challenged the transplant practice worldwide. Innovative telehealth solutions have emerged allowing safe and efficient outpatient care, delineating the future transplant practice in the post-COVID-19 era. As the pandemic continues and new, more infectious variants of the virus emerge, identification of risk factors for infection may allow to risk stratify patients and tailor prevention strategies and prioritize vaccination in patients at highest risk.

The early decision to postpone nonurgent transplant programs has been accompanied by a drastic drop of organ procurement around the world. Such position has been questioned by the risk of mortality on the waiting list, and huge efforts have been made to settle efficient mitigating strategies to overcome these ethical issues. Ideal strategies still have to be defined, and risk/benefit assessment should be discussed on a case-by-case basis within the transplant team. Even more uncertain is the management of immunosuppression and how it affects the risk of infection, mortality, and, possibly, response to vaccination. This might be very important, as preliminary

data among 436 transplant recipients that received either BNT162b2 vaccine (Pfizer-BioNTech) or the mRNA-1273 vaccine (Moderna) suggest that the antibody immunity may be lower than in the general population, as evident by only 17% detection of antibody against the spike antigen after first dose of the vaccine [25].

The need for remote monitoring of graft function has further highlighted the importance of noninvasive biomarkers of acute rejection. Despite the approval by the Food and Drug Administration of a few assays, this still largely represents an unmet need that should also be adequately addressed in the post-COVID-19 period of transplant medicine.

Optimal protection of kidney transplant recipients during COVID-19 outbreak is an evolving concept, and more studies are required to understand special needs of this fragile population. Through an extremely challenging path, this pandemic forced the transplant community to revisit strategies and priorities. Once the viral spread will be under control, these challenges may ultimately result in a better care of transplanted individuals.

Conflict of Interest Statement

The authors declare that they have no conflict of interest to disclose. P.C. is supported by NIH NIAID grant 3U01AI063594-17S1.

References

- 1 Green M. Introduction: infections in solid organ transplantation. *Am J Transplant*. 2013; 13(Suppl 4):3–8.
- 2 Gandolfini I, Delsante M, Fiaccadori E, Zaza G, Manenti L, Degli Antoni A, et al. COVID-19 in kidney transplant recipients. *Am J Transplant*. 2020;20(7):1941–3.
- 3 Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and kidney transplantation. *N Engl J Med*. 2020; 382(25):2475–7.
- 4 Cravedi P, Mothi SS, Azzi Y, Haverly M, Farouk SS, Pérez-Sáez MJ, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant consortium. *Am J Transplant*. 2020;20(11):3140–8.
- 5 Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York city. *N Engl J Med*. 2020;382(24):2372–4.
- 6 Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. *JAMA*. 2020;323(21):2195–8.
- 7 Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020;323(24):2493–502.
- 8 Rinaldi M, Bartoletti M, Bussini L, Pancaldi L, Pascale R, Comai G, et al. COVID-19 in solid organ transplant recipients: no difference in survival compared to general population. *Transpl Infect Dis*. 2020:e13421.
- 9 Cravedi P, Schold JD, Safa K, Kates OS, Elfadawy N, Mannon RB, et al. The COVID-19 pandemic: a community approach. *Clin Transplant*. 2020;34(11):e14059.
- 10 Willicombe M, Gleeson S, Clarke C, Dor F, Prendecki M, Lightstone L, et al. Identification of patient characteristics associated with SARS-CoV-2 infection and outcome in kidney transplant patients using serological screening. *Transplantation*. 2021;105(1):151–7.
- 11 Prendecki M, Clarke C, Gleeson S, Greathead L, Santos E, McLean A, et al. Detection of SARS-CoV-2 antibodies in kidney transplant recipients. *J Am Soc Nephrol*. 2020;31(12): 2753–6.
- 12 Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2020;8(10):823–33.
- 13 Perez-Guzman PN, Daunt A, Mukherjee S, Crook P, Forlano R, Kont MD, et al. Clinical characteristics and predictors of outcomes of hospitalized patients with COVID-19 in a multi-ethnic London NHS Trust: a retrospective cohort study. *Clin Infect Dis*. 2020.
- 14 Chan S, Pascoe EM, Clayton PA, McDonald SP, Lim WH, Sypek MP, et al. Infection-related mortality in recipients of a kidney transplant in Australia and New Zealand. *Clin J Am Soc Nephrol*. 2019;14(10):1484–92.
- 15 Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global rheumatology alliance physician-reported registry. *Ann Rheum Dis*. 2020;79(7):859–66.

- 16 Hartzell S, Bin S, Benedetti C, Haverly M, Gallon L, Zaza G, et al. Evidence of potent humoral immune activity in COVID-19-infected kidney transplant recipients. *Am J Transplant.* 2020;20(11):3149–61.
- 17 Amanat F, Stadlbauer D, Strohmaier S, Nguyen THO, Chromikova V, McMahon M, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. *Nat Med.* 2020; 26(7):1033–6.
- 18 Premkumar L, Segovia-Chumbez B, Jadi R, Martinez DR, Raut R, Markmann A, et al. The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. *Sci Immunol.* 2020;5(48):5.
- 19 Avanzato VA, Matson MJ, Seifert SN, Pryce R, Williamson BN, Anzick SL, et al. Case study: prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised individual with cancer. *Cell.* 2020;183(7):1901–e9.
- 20 Chen Y, Zuiani A, Fischinger S, Mullur J, Atyeo C, Travers M, et al. Quick COVID-19 healers sustain anti-SARS-CoV-2 antibody production. *Cell.* 2020;183(6):1496–e16.
- 21 Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. *Nature.* 2020.
- 22 Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-based Covid-19 vaccine candidates. *N Engl J Med.* 2020; 383(25):2439–50.
- 23 Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med.* 2020;383(25):2427–38.
- 24 Arora S, Kipp G, Bhanot N, Sureshkumar KK. Vaccinations in kidney transplant recipients: clearing the muddy waters. *World J Transplant.* 2019;9(1):1–13.
- 25 Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. *JAMA.* 2021.