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EDITORIAL

Transplanting COVID-19 positive donors: Expanding our experience to widen the donor pool

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As we enter the third year of the COVID-19 pandemic with the unfortunate realization that complete eradication of SARS-CoV-2 may be impossible, we must transition from a pandemic response to life with COVID-19. As part of this new normal, a better understanding of the selection and management of SARS-CoV-2-positive donors for heart and lung transplantation is crucial. In this issue of the *Journal of Heart and Lung Transplantation*, Eichenberger et al share their important experience with transplanting thoracic organs from SARS-CoV-2-positive donors.[1] The authors performed 14 thoracic transplants in 13 recipients using organs from infected donors. None of the recipients or healthcare members acquired COVID-19, no recipients suffered unexpected acute rejection, and recipient survival was 92%.

Balancing the benefits of expansion of the donor pool with risks of infection transmission to transplant recipients is a major challenge. When transplanting organs from donors with a positive SARS-CoV-2 reverse transcription (RT)-PCR, one must consider: (1) the extent of donor organ involvement from COVID-19; (2) the variability of testing strategies to predict donor transmission; (3) the effectiveness and accessibility of proven treatments for this potentially lethal condition; (4) the impact of vaccination on this risk equation; and (5) the potential for the transplant recipient to become a vector for viral transmission.[2]

SARS-CoV-2 is primarily isolated from the respiratory tract,[3] but it has also been isolated from blood (in up to 15% of cases[4]) and all organs.[5] However, since the viral load detected in blood samples of COVID-19 patients is typically low, the potential for hematogenous transmission of SARS-CoV-2 is also thought to be low, especially as the virus has not been isolated from blood in cell culture. Indeed, despite the observation of SARS-CoV-2 RNAemia, no transmission through a blood product or stem cell transfusions have been reported.[6-9]

These observations are cause for cautious optimism, and in sparse reports of extra-thoracic solid organ transplantation from SARS-COV-2-infected donors into non-infected recipients, including 24 kidney and 7 liver transplants, no transplant recipients developed COVID-19.[10] In these cases, recipients likely did not have significant immunity against SARS-CoV-2, as reported rates of vaccination and prior COVID-19 infection were low. Still, it is difficult to broadly apply these reports to general practice as peri-transplant care differed. Some recipients were prophylactically treated with COVID-19 therapy (i.e., lopinavir−ritonavir and hydroxychloroquine, remdesivir, casirivimab/imdevimab, and convalescent plasma), and the impact of these therapies on donor transmission is not clear.

Nonetheless, the successful outcomes of these liver and kidney transplant recipients must be tempered by observations in lung transplant recipients. Donor-derived transmission of SARS-CoV-2 in lung transplant recipients has been reported in 3 cases, despite negative SARS-CoV-2 PCR from nasopharyngeal samples, and all recipients developing severe COVID-19, leading to death in one.[11,12] In 2 of these cases, retrospective PCR testing of stored bronchoalveolar lavage (BAL) fluid or intraoperative BAL were positive, highlighting one of the many challenges in assessing donors for organ transplantation: the source of the SARS-CoV-2 specimen. The viral load from lower respiratory tract samples might be higher, peak later, and persist longer than those from the upper respiratory tract. The converse is also true: high concentrations of virus can be detected in the nasal passages of infected individuals regardless of their clinical manifestations.[13] Thus, symptom-based testing and restrictions on the timeline/time frame for consideration of donor organs alone are not adequate to control transmission of the virus.

In the context of these previously published reports, the series presented in the manuscript of Eichenberger et al

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serves to highlight that the donor pool can be expanded by implementing appropriate surveillance strategies. In their series, lower respiratory tract testing for SARS-CoV-2 was performed on lung donors on the day of organ donation, in line with the April 2021 International Society of Heart and Lung Transplantation (ISHLT) COVID-19 Task Force recommendations for deceased cardiothoracic donor screening for SARS-CoV-2 RNA by upper respiratory tract sampling with nucleic acid amplification testing (NAAT) within 72 hours of procurement and, for lung donors, acquisition of a deep respiratory specimen for SARS-Co-V-2 RNA.[14]

While the findings of Eichenberger et al show great promise, many unanswered questions remain. For example, one challenge in donor risk assessment is assay variability. The available commercial and laboratory SARS-CoV-2 RNA assays have a wide range of gene targets, analytical sensitivities, throughput, automation, turnaround time, and accepted specimen types. Most importantly, management decisions often hinge upon the SARS-CoV-2 cycle threshold values, which can vary by the assay performed. Consequently, the cycle threshold value as a universal threshold for infectivity is limited.

Another challenge of RT-PCR testing is that it does not differentiate between the persistence of viral RNA, viral shedding, and ongoing viral replication, and thus RNA-positive samples could represent the detection of genomic fragments rather than an actively replicating virus. This suggests that the mean period of infectiousness and the risk of transmission may not have to be as long as 20 days from the onset of symptoms or PCR positivity, as in the series of Eichenberger et al and in accordance with the April 2021 ISHLT taskforce recommendations.[14] While a shorter window may further broaden the pool of potential donors, it is also important to note that imaging evidence of COVID-19 pneumonia, even before development of symptoms or a positive PCR test, could be considered for assessment of COVID-19 infectiousness in a potential thoracic organ donor.[2,14]

The emergence of new variants poses further challenges, as incubation time for these new variants appears to be shorter,[15] suggesting the recommended interval of <72 hours between RT-PCR testing and lung procurement may be too long. One solution to narrow the window of uncertainty between the last RT-PCR and lung procurement and thereby reduce the likelihood of donor-derived viral transmission is to use point-of-care tests (POCTs) (rapid antigen test or nucleic acid amplification test) on BAL samples at the time of lung procurement.[9] Similarly, the duration of infectiousness might also be impacted by new SARS-CoV-2 variants and the diagnostic test used, making a 20 day window to define infectiousness and risk of transmission too short or (more likely) too long.

To date, the impact of vaccination on the transmissibility of SARS-CoV-2 is not well defined, and the issue is further complicated by the higher transmissibility of the new variants. While vaccination may reduce viral transmission and subsequent infection by early variants of SARS-CoV-2,[16] transmission of more recent variants from vaccinated index cases is similar to that from unvaccinated individuals.[17] A prospective cohort study in the United Kingdom on community transmission of SARS-CoV-2 demonstrated that 2-dose vaccinated individuals with breakthrough infections have peak viral loads similar to that of unvaccinated cases and can efficiently transmit infection, including to 2-dose vaccinated contacts.[17] Other studies have shown that peak viral titers in the upper airways and culturable virus are similar in vaccinated and unvaccinated individuals.[18,19] Nevertheless, viral load appears to decline at a faster rate in individuals who have been vaccinated, suggesting that the window of transmissibility may be reduced by SARS-Cov-2 vaccination.[17] These factors could impact the window of potential transmissibility of a SARS-CoV-2-positive organ donor, but there is insufficient evidence to provide specific recommendations on how donor vaccination status might affect the risk to potential recipients.

Expanding the donor pool wisely is an important endeavor, and the lessons learned are relevant to other donor infections, such as tuberculosis or hepatitis C or B viruses.[3] These factors will also be essential in considering xenotransplantation, where novel pathogens such as porcine endogenous retroviruses, may impact organ transplant recipients.

Eichenberger et al are to be congratulated for offering the most extensive experience to date on transplantation of SARS-CoV-2-positive thoracic organ donors. Nonetheless, there is much we still do not know: How is donor transmission of SARS-CoV-2 impacted by donor vaccination and new variants? What are the longer-term consequences of transplanting an organ with evidence of COVID-19 infection? Is there a risk of prolonged persistence of replication-competent virus and the risk of SARS-CoV-2 transmission in the immunocompromised transplant recipients?[20] The findings of Eichenberger et al are cause for tempered optimism, but there is much to learn as we cautiously apply the findings to our clinical practice.

Ultimately, new outbreaks of emerging infections with novel pathogens will likely continue to challenge organ transplantation. In the transition from pandemic response to living with the virus, the consideration of COVID-19-positive donors will allow us to maximize the benefits of thoracic organ transplantation. As we obtain answers to questions regarding varying assays, vaccination status, and viral variants, there will be a pressing need to nimbly revise transplant policies to reflect this new and emerging evidence.[21] In this manner, we can fulfill our mandate to maximize the benefit of organ transplantation while doing no harm.

Disclosure statement

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