Clinical Infectious Diseases

EDITORIAL COMMENTARY

Coronavirus Disease 2019 (COVID-19), Organ Transplantation, and the Nuances of Immunomodulation: Lessons Learned and What Comes Next

Ghady Haidar[1,2]

[1]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA, and [2]Division of Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

(See the Major Article by Kates et al on pages e4090–9.)

Keywords. COVD-19; solid organ transplant; immune response; organ donation.

The coronavirus disease 2019 (COVID-19) pandemic has caused a seismic shift in transplant practices. Many centers have suspended live donor transplants, and most have enforced significant restrictions to their deceased donor programs [1]. Because of early observations suggesting a role of proinflammatory cytokines in the pathogenesis of severe COVID-19 [2], a prevailing thought has been that the anti-inflammatory effects of immunosuppressive medications may paradoxically diminish disease severity in solid organ transplant (SOT) recipients with COVID-19. There is precedent in the literature to support this line of speculation. For instance, kidney and liver transplant recipients with sepsis were shown to have lower mortality rates compared to nontransplant patients [3], which was thought be partially due to a dampening of the destructive aspects of sepsis by immunosuppressive agents. Additionally, calcineurin inhibitors modulate the expression of opportunistic infections such as cryptococcosis, protecting against mortality in SOT recipients [4]. However, these optimistic notions were at odds with our knowledge that SOT recipients with respiratory viral infections such as influenza develop more severe complications than the general population. Additionally, transplant patients frequently suffer from the same comorbidities that have been associated with detrimental outcomes in COVID-19. Nonetheless, and despite early hints that mortality in SOT recipients may be high, the outcomes of SOT recipients with COVID-19 have remained ill defined.

In this issue of *Clinical Infectious Diseases*, Kates and colleagues describe the outcomes of 482 SOT recipients with COVID-19 across over 50 transplant centers. Although the majority of patients were kidney transplant recipients, this is nonetheless the largest study of SOT and COVID-19 to date and confirms the ominous findings from smaller cohorts: in short, SOT recipients with COVID-19 are at high risk for complications and death. The authors demonstrate that 78%, 34%, and 27% of SOT recipients with COVID-19 require hospitalization, intensive care, and mechanical ventilation, respectively. Additionally, the inpatient mortality rate was ~20%, which is similar to the pooled weighed mortality rate of ~19% (range 8–33%) reported in studies from the general population with a similar median age and prevalence of comorbidities. Indeed, over 90% of SOT recipients with COVID-19 had chronic medical conditions, and nearly a third were >65 years of age. The authors should be commended for appropriately navigating the epidemiological quagmire of case fatality rates in COVID-19, as comparisons with studies of younger and healthier patients—such as the Chinese Center for Disease Control study, which reported a mortality rate of 2.3% [5]—would not have been suitable. The only predictors of mortality in the current study were age (>65 years), heart failure, chronic lung disease, obesity, pneumonia, and lymphopenia. In contrast, the "net state of immunosuppression" had no impact on mortality, neither did time from transplant. Thus, although morbidity and mortality related to COVID-19 in SOT recipients are substantial, they appear to be driven by age and underlying medical conditions and unaffected by immunosuppression, corroborating the results of other studies in the general population. The study included only 30 lung transplant recipients and was therefore unable to assess whether mortality in these patients is greatest (as is the case with

Received 1 August 2020; editorial decision 6 August 2020; accepted 10 August 2020; published online August 11, 2020.

Correspondence: G. Haidar, Division of Infectious Diseases, 3601 Fifth Ave, Falk Medical Bldg, Ste 5B, Pittsburgh, PA 15213 (haidarg@upmc.edu).

Clinical Infectious Diseases® 2021;73(11):e4100–2

DOI: 10.1093/cid/ciaa1193

sepsis [3]) or whether COVID-19 precipitates acute or chronic lung allograft rejection. Furthermore, because all laboratory testing was done as standard of care, the study could not evaluate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viremia or the duration of SARS-CoV-2 polymerase chain reaction (PCR) positivity, which may be longer than that of nontransplant patients. Although prolonged viral shedding is common and does not imply infectivity [6], critically ill SOT recipients who are unable to control viral replication may potentially serve as a source of continued viral transmission. Finally, patients received various interventions for COVID-19, and no conclusions can be made about the efficacy of any of these therapies.

Several other key observations from this study warrant special mention. First, fever, which was defined as a temperature of >38.1°C, and which is erroneously perceived to be a universal finding in COVID-19, developed in only 55% of patients. Second, the manifestations of COVID-19 were protean and included a plethora of "atypical symptoms," with fatigue or gastrointestinal symptoms occurring in ~50% of patients. Clinicians must therefore have a low threshold for performing PCR testing for SARS-CoV-2 in SOT recipients and must not discount the possibility of COVID-19 in afebrile patients or those with "atypical symptoms." Third, most SARS-CoV-2 infections were community acquired, and no donor-derived infections occurred. The lack of donor-derived infections is a testament to the excellent guidance by the American Society of Transplantation (AST) Infectious Diseases Community of Practice regarding donor testing [7] and the rapid adoption of these guidelines by organ procurement organizations. Fourth, and perhaps most surprisingly, was the paucity of superinfections and fungal infections, although additional studies will be needed to define the incidence of "post-COVID-19 invasive aspergillosis."

Now that the characteristics and outcomes of SOT recipients with COVID-19 have been defined, the question is "what comes next?" How can we synthesize the deluge of COVID-19 knowledge into therapeutic interventions? The key lies in developing a nuanced understanding of the pathogenesis of COVID-19. However, this may prove to be a herculean challenge because of the heterogeneity of the host-pathogen interactions in COVID-19. Indeed, a recent study of deep immune profiling of patients with COVID-19 revealed several "immunotypes" ranging from robust CD4 and/or CD8 responses to minimal lymphocyte responses to infection [8]. Furthermore, the mortality benefit of dexamethasone among patients with COVID-19 who require supplemental oxygen, particularly those who received the drug after their first week of illness [9], lends some credence to the notion that immunosuppressants may ameliorate outcomes after transplant, and suggests that immunopathology drives tissue damage in the later stages of illness. These observations can inform the design of trials of immunosuppression management in SOT. Kates et al showed that immunosuppression was modified in 70% of patients, and that the antimetabolite (mycophenolate or azathioprine) was stopped in 56% of patients. Although this mirrors clinical practice in other infections, it is rational to speculate whether mortality in SOT recipients with COVID-19 could have been attenuated by less aggressive immunosuppression modification, given what is now known about dexamethasone.

Several issues unique to transplantation will require reevaluation as the pandemic evolves. First, programs need to be flexible in how they adapt to rising cases in their regions, relying on a tiered approach for adjusting transplant activity based on the burden of COVID-19 in the region and hospital. Moreover, centers that have remained unaffected by the pandemic may need to resort to temporary cessation of transplants if COVID-19 cases surge. Second, centers performing preoperative SARS-CoV-2 PCR screening for asymptomatic transplant candidates must publish their experiences. These studies should focus on the impact that canceling cases due to positive PCRs has on waitlist mortality, and on the optimal timing of reactivating a SARS-CoV-2-positive transplant candidate. Third, universal SARS-CoV-2 testing of deceased donors, which is currently recommended by the AST [7], may one day be relaxed as herd immunity develops and once SARS-CoV-2 becomes a seasonal circulating virus. Finally, although it is permissible to use organs other than lungs and intestines from donors with influenza, whether organs from a donor with COVID-19 can ever be transplanted warrants careful evaluation. Issues to consider include (a) the repercussions of SARS-CoV-2 viremia (which is uncommon and of unclear significance) [2] in the deceased donor and (b) whether the use of any organ is safe, given the dissemination of SARS-CoV-2 to kidneys and other organs in some patients [10]. Current guidelines recommend against the use of donors with a history of COVID-19 unless a negative SARS-CoV-2 PCR result is documented [7]. Because chronic nasopharyngeal shedding of ostensibly inert SARS-CoV-2 appears to be common [6], these recommendations may be modified in the coming years. Once an effective vaccine is developed and mass-administered, these paradigms and many others will need to be revisited.

In the past decades, the transplant community has had to respond to SARS-CoV, pandemic influenza H1N1, Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola virus, Zika virus, and others. Although COVID-19 is a pandemic of unparalleled proportions, transplant providers have learned to adjust to a new normal. Looking beyond the current crisis, transplant research efforts should focus on pathogenesis and virology, immunosuppression strategies, donor and recipient screening issues, and

vaccine and drug trials in SOT. Finally, we must prioritize protecting SOT recipients from SARS-CoV-2 infection by enforcing social distancing, implementing universal masking, and utilizing telemedicine services to provide care.

Notes

Financial support. This work was supported by the National Institutes of Health through grant number KL2TR001856 awarded to G. H.

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

The manuscript has not been previously published nor is it being considered for publication elsewhere.

References

1. Boyarsky BJ, Po-Yu Chiang T, Werbel WA, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. Am J Transplant **2020**; 20:1809–18.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet **2020**; 395:497–506.
3. Donnelly JP, Locke JE, MacLennan PA, et al. Inpatient mortality among solid organ transplant recipients hospitalized for sepsis and severe sepsis. Clin Infect Dis **2016**; 63:186–94.
4. Singh N, Alexander BD, Lortholary O, et al. *Cryptococcus neoformans* in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. J Infect Dis **2007**; 195:756–64.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA **2020**; 323:1239–42. doi:10.1001/jama.2020.2648
6. Wolfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-19. Nature **2020**; 581:465–9.
7. Recommendations and Guidance for Organ Donor Testing. Updated July 8. Available at: https://www.myast.org/sites/default/files/sites/default/Donor%20Testing%20Document_Updated_2020_0708.pdf. Accessed 27 July 2020.
8. Mathew D, Giles JR, Baxter AE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science **2020**; eabc8511. doi:10.1126/science.abc8511
9. Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19: preliminary report. N Engl J Med **2020**. doi:10.1056/NEJMoa2021436
10. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int **2020**; 98:219–27.