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Covid-19 in recipients of heart and lung transplantation: Learning from experience

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As of May 2021, SARS-CoV-2 is estimated to have infected 161 million people worldwide and been responsible for over 3 million deaths.[1] Early in the pandemic, the impact of COVID-19 on solid organ transplant recipients was not well established, and initial experience suggested the presentation of COVID-19 in solid organ transplant recipients was similar to that of nontransplant patients.[2,3] However, in subsequent reports, heart and lung transplant recipients fared worse than nontransplant patients, with an observed mortality of 20% to 30%.[4,5] Two articles in the current issue of the *Journal of Heart and Lung Transplantation* offer greater insight into the clinical characteristics and outcomes of heart[6] and lung[7] transplant recipients infected with SARS-CoV-2.

COVID-19 in heart transplantation

Patients with heart failure had been significantly impacted by the SARS-CoV-2 pandemic given their increased risk of mortality[8] and the reduction in heart transplant volume[9] though, fortunately, concerns of COVID-19-related myocarditis appear unfounded[10] and donor-to-recipient transmission in heart transplant patients has not been reported. However, the unique clinical characteristics, risk factors, and outcomes of heart transplant recipients infected with SARS-CoV-2 is not well characterized and the study in this issue of the *Journal of Heart and Lung Transplantation* by Genuardi and colleagues offers important observations regarding the clinical course, immunosuppression and outcomes.[6]

In this, the largest descriptive series to date, of 99 consecutive heart transplant recipients with SARS-CoV-2 infection at 11 centers, COVID-19 affected a disproportionate number of patients who self-identified as Black race (42%) while the overall transplant population at these 11 centers comprised only 15% Black transplant recipients. This observation is consistent with the epidemiology of COVID-19[11] and further supports the notion that social disparities may negatively affect outcomes even in a highly selected population of heart transplant recipients with access to specialized care and close follow-up. Notably, atypical symptoms were common in heart transplant recipients: 43% of patients had no fever and while cough was present on presentation in 49%, gastrointestinal symptoms were as prominent, occurring in 46% of patients.

About two-thirds of heart transplant recipients with COVID-19 required hospitalization and one-quarter had severe illness, defined as need for mechanical ventilation, new renal replacement therapy, or use of vasoactive agents for blood pressure support. One-quarter of those hospitalized ultimately died; the overall case fatality rate was 15%. While these outcomes are sobering, it is important to note that deaths were due to COVID-19 complications; only 1 patient had heart failure and none of the deaths were attributed to cardiac dysfunction, and severe outcomes and death were not associated with race.

Perhaps the most useful observation of this study is the impact of immunosuppressive agents on outcomes. When compared to a regimen of calcineurin inhibitor + antimetabolite, the use of a proliferation signal inhibitor use was associated with a 6.8-fold increased risk of severe disease and use of prednisone was associated with 7.3-fold risk of severe disease and 17.8-fold increased risk of death.

The current study by Genuardi et al. offers greater insight into the evaluation and management of patients with

The only source of knowledge is experience. −Albert Einstein

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COVID-19: the importance of a high index of suspicion in heart transplant recipients with gastrointestinal symptoms regardless of fever, as well as consideration for adjustment of immunosuppression with temporary cessation of proliferation signal inhibitors in infected patients, and for enhanced preventive strategies in the Black transplant community. And there may be some cause for hope: the case fatality rate of 15% is lower than that observed in other studies,[12-14] which is multifactorial but likely due in part to evolution in management strategies and because hospital supplies were not as constrained as during the hyperacute surges in parts of Europe in early 2020.

COVID-19 in lung transplantation

The SARS-CoV-2 pandemic has similarly impacted the process of lung transplantation globally, with dramatic reductions in transplant volume,[15] the ever-present risk of donor-to-recipient transmission,[16] the advent of lung transplantation for severe COVID-19,[17] and the potential for significant morbidity and mortality in patients with end-stage lung disease acquiring infection before[18] or after[4] transplantation. In this issue, Mohanka and colleagues describe their experience in 25 lung transplant recipients from Dallas, Texas infected with SARS-CoV-2.[7] Their patient cohort, representative of lung transplant cohorts around the world, exhibited a median age of 60 (range 20-73) and the majority were male with a history of restrictive lung disease as the indication for transplantation. Of the 25 patients, 88% reported symptoms consistent with lower, rather than isolated upper, respiratory tract involvement (productive cough, wheezing, shortness of breath), 57% experienced significant allograft dysfunction (forced expiratory volume in 1 second [FEV_1] decline >10%), and 60% had opacities on chest radiograph.

Lung transplant recipients were at risk for poor outcomes: over one-third developed new or worsening respiratory failure requiring high-flow oxygen, noninvasive ventilation or intubation and 3 (12%) patients died.[7] Risk factors for respiratory failure included lower baseline FEV_1, the presence of parenchymal opacities on admission chest radiograph, and longer time between symptom onset to initiation of remdesivir or convalescent plasma.

Notably, one-third of survivors were readmitted at a median of 5 days post discharge and one-quarter of those had new respiratory failure. Even more concerning, among those patients with available post-COVID-19 spirometry performed 4 weeks or more after the illness onset, half had >10% loss in forced vital capacity or FEV_1 and most survivors reported worsening of functional status. The impact of COVID-19 was far worse than that of respiratory syncytial virus (RSV) infection; in a historical cohort of 36 lung transplant recipients with RSV 2016-2018, 97% survived.

Although the study by Mohanka et al. is small, it offers hope as outcomes are better than originally reported in lung transplant recipients.[4,5,19-21] Compared with earlier reports of mortality approaching 30%, in a more current series of 2307 solid organ transplant recipients with COVID-19 (8% lung transplant and 11% heart transplant recipients), 30-day mortality was 4.8%.[22] However, while the mortality of COVID-19 in lung transplant recipients may not be as high as originally feared, ongoing issues remain regarding the potential for long-term effects on allograft function, including acceleration of chronic allograft loss, as seen with other viral respiratory tract infections. In addition, the ideal adjustment of immunosuppression regimens to mitigate disease severity has not been established.

Lessons learned

In highly vaccinated communities throughout the world, the worst of the COVID-19 pandemic may be behind us. In the United States, at a time when 60% of adults have received at least one vaccination, the 7-day average of daily new cases dropped 81% between January and May 2021.[23] In Israel, where over 90% of adults over 60 years of age have been vaccinated, there have been fewer than 10 Covid-19 fatalities per day since April 2021.[24] But does this optimism borne of vaccination apply to transplant recipients?

Unfortunately, this optimism must be tempered by the evidence of immune paresis in transplant recipients.[25] Heart transplant and lung transplant patients who have received mRNA vaccines mount an inadequate antibody response[26,27] and may still develop severe infection after vaccination.[28]

So as we look to the future of a COVID-19-endemic world, studies like those of Genuardi et al.[6] and Mohanka et al.[7] offers crucial experience so that we may best care for our heart transplant and lung transplant recipients. As the two articles indicate, outcomes may be improving over time and we now have some insight, for heart transplant recipients, into potentially beneficial adjustments in immunosuppression to mitigate disease severity.

We await with anticipation the knowledge that comes from further experience, including understanding the optimal timing of vaccination and potential adjustment of immunosuppression in transplant recipients to maximize the vaccine immune response. Fortunately, studies evaluating responses to additional vaccine doses and T-cell response are currently underway. Until such knowledge is available, the best way to protect transplant recipients is through maintenance of social distancing and masking, and vaccination[29]—not only vaccination of said transplant recipients, but of all eligible individuals—to prevent viral transmission and subsequent infection in this vulnerable population.

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