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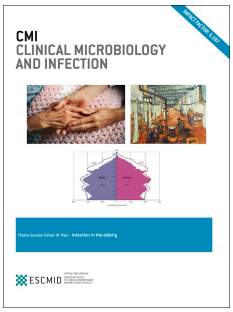

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Luther Bartelt, David van Duin

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An Overview of COVID-19 in Solid Organ Transplantation

Luther Bartelt[1,2], David van Duin[1]

1. Division of Infectious Diseases, Department of Medicine, University of North Carolina at Chapel Hill, North Carolina, United States
2. Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, North Carolina, United States

*Corresponding author:

David van Duin, MD, PhD, Division of Infectious Diseases, CB 7030, University of North Carolina, 130 Mason Farm Road, Chapel Hill, North Carolina 27599, United States of America

Telephone: 919-843-2200, Fax: 919-966-6714

Email: david_vanduin@med.unc.edu

ABSTRACT

Background

The COVID-19 pandemic has influenced the field of solid organ transplantation (SOT) in many ways. COVID-19 has led to programmatic impacts and changes in donor and recipient selection. Several studies have evaluated the course, optimal treatment, and prevention of COVID-19 in SOT recipients.

Objective

To review the literature on COVID-19 in SOT recipients.

Sources

PubMed, Web of Science, and Google Scholar were searched. The search was restricted to articles published between January 1, 2019, and December 1, 2021.

Content

The COVID-19 pandemic initially led to a decreased volume of solid organ transplants. However, transplant volumes at most centers have rebounded. Donor selection remains an incompletely defined issue. Several reports suggests that donor-derived SARS-CoV-2 infections occur only in lung transplant recipients, and that other organs from SARS-CoV-2 PCR-positive donors could potentially be safely used. However, these data are limited to case series. Transplantation for end-stage lung disease after COVID-19 infection is increasingly common and has been performed with acceptable outcomes. In acute COVID-19 in a transplant candidate, transplantation should be delayed when feasible. After adjustment, mortality after COVID-19 appear similar in SOT recipients as compared to the general population, with notable increased use of anti-viral and anti-inflammatory treatment options. Prevention of COVID-19 is key in SOT recipients.

Vaccination of SOT recipients and anyone who is in contact with SOT recipients is one of the cornerstones of prevention. Non-pharmacological interventions such as face coverings, hand hygiene, and physical distancing remain ever important as well.

Implications

The COVID-19 pandemic continues to have an important impact on SOT candidates and recipients. Prevention of infection is the most important measure, and requires careful attention to approaches to vaccination, and messaging of the ongoing need for face coverings, physical distancing, and hand hygiene.

Background

The COVID-19 pandemic has impacted the field of solid organ transplantation (SOT) in direct and indirect ways. Infection with SARS-CoV-2 has led to many hospitalizations, intensive care unit (ICU) admissions, and deaths among SOT recipients around the world. This enormous toll is further exacerbated by the longer-term effects of SARS-CoV-2 infection, which include decline in graft function, graft loss, and rejection [1, 2]. Furthermore, there is concern over increased risk of secondary infections after COVID-19 in SOT recipients. These secondary infections may include other viral, bacterial, mycobacterial, and fungal infections [3].

In addition to these direct effects, the indirect effects on the ability of transplant centers to perform transplantation and to optimally care for their patients has been impacted by the COVID-19 pandemic. Especially early during the pandemic, numbers of transplants performed decreased in most transplant centers in reaction to the rapid spread of SARS-CoV-2 [4]. The rate of transplantation has rebounded. Overall, an increased number of transplants were performed in 2021 in the US, as compared to 2019 [5]. However, there is ongoing strain on the healthcare system which also inevitably impacts the care of SOT recipients. These strains include limited availability of ICU-level care, and inability of transplant centers to accept transfers of patients from other centers due to lack of bed availability. Furthermore, the COVID-19 pandemic has had a disproportionate impact on infection prevention and control efforts. As personnel, resources, and attention are rightfully directed towards control of COVID-19, many centers have experienced increased rates of other nosocomial infections [6]. Of note, the incidence of *Clostridioides difficile* infections during the pandemic has remained

overall stable with some centers showing a decrease in numbers, potentially because of measures put in place to limit spread of SARS-CoV-2 [6-8].

In this review, we will summarize the literature on COVID-19 and solid organ transplantation, with a focus on various phases of transplant: donors with COVID-19, transplantation in recipients with COVID-19, and COVID-19 after transplantation. Overall treatment considerations will not be discussed as they were recently reviewed elsewhere and are subject to frequent changes. In general, there is no evidence to support a different approach to antiviral treatment of COVID-19 in SOT recipients as compared to other patients with COVID-19 [9]. Some SOT-specific COVID-19 management questions such as management of immunosuppressive agents are discussed.

Sources

We conducted a literature search for peer-reviewed literature focusing on COVID-19 in solid organ transplantation, using search terms “COVID-19”, “SARS-CoV-2”, “SOT” “transplant”, “transplantation”. PubMed, Web of Science, and Google Scholar were searched. The search was restricted to articles published between January 1, 2019, and December 1, 2021. LAB and DVD each performed an independent literature search. Full-text articles were retrieved for detailed assessment of suitability, risk of bias and data extraction. Cross-references of interest were included.

Impact on transplant programs

As SARS-CoV-2 swept the globe, healthcare systems were forced to rapidly shift operations to accommodate the influx of patients admitted with severe COVID-19. Consequently, intensive care unit capacity, trained staff, and equipment necessary for immediate care after transplant was limited and the number of SOT performed declined worldwide. Data from regional and national databases such as the United Network for Organ Sharing (UNOS) in the United States estimate between 40-90% reductions in deceased donor transplantations in the first 6 weeks of the pandemic, with similar decreases seen in other parts of the world [4, 10, 11]. Although the greatest reductions were seen in communities experiencing the most rapid surges, the need to establish new protocols for donor selection and safe organ procurement contributed to decreases in all programs, including those with relatively low local prevalence of COVID-19. The effect was seen across all organ groups – i.e. kidney, heart, liver, and lung – with the greatest impact on kidney transplantation [4]. After public health and infrastructure adjustments were established, the second half of 2020 and 2021 saw a rebound in SOT completions, with many programs returning to and in some cases exceeding pre-pandemic capacity [5]. As of the writing of this review, the United States is on target to surpass 40,000 total transplants in 2021 for the first time. Despite the public health and infrastructure efforts to restore SOT program capacities, overall mortality among waitlisted kidney transplant candidates was 24% higher in 2020 than 2019, with 11% of total deaths directly attributable to COVID-19 [12].

COVID-19 in potential solid organ transplantation donors

The same principles of SARS-CoV-2 transmission through respiratory secretions in general population studies also apply to risk of donor-to-recipient transmission in solid organ transplantation. All reported donor-derived infections have occurred in lung transplant recipients [13]. In lung transplant, viral genome sequencing has confirmed donor-derived transmission despite negative nasopharyngeal testing prior to organ procurement [14]. Multiple transmissions from infected donors have demonstrated that upper respiratory nasopharyngeal sampling alone is not sufficient to prevent donor-derived transmission in lung transplantation [13]. In contrast, although SARS-CoV-2 RNA is detectable in multiple non-respiratory tissues, and viral particles can be identified in blood products, there have been no reported cases of donor-derived infections in non-lung organ recipients despite donors with lower respiratory samples positive for SARS-CoV-2 [13, 15, 16]. In one case, a deceased kidney donor who died with active COVID-19 was successfully used [17]. In another reported case, a living liver donor developed COVID-19 symptoms 3 days after donation, but the unvaccinated recipient did not develop symptoms, and tested negative on post-operative days 4 and 5 [18]. Taken together, these reports of successful transplantation of non-respiratory organs from actively infected donors suggest that non-respiratory organ transplantation might be safely performed despite active infection. However, the experience remains limited and there are insufficient data to guide protocolized acceptance of organs despite active donor infection. Furthermore, it is not known whether pre-transplant vaccination in transplant candidates is sufficient to prevent donor-derived SARS-CoV-2 infection.

Most organ procurement networks recommend respiratory nucleic acid testing (NAT) for all potential donors, regardless of COVID-19 symptoms [19]. NAT is preferred to rapid antigen testing given the greater sensitivity for detecting SARS-CoV-2 RNA. However, NAT turnaround times can vary greatly between laboratories and regions and the resulting time-lag between testing and organ procurement could potentially result in a misclassified donor converting to NAT positive by the time of organ procurement [20]. Most centers therefore require NAT within 72 hours of organ procurement. Emerging data suggest that non-lung organs from donors with COVID-19 may potentially be safely transplanted, provided the organ is otherwise in good condition [21]. While NAT have low false negative rates, it is important to note that these tests are not designed to detect replication competent virus that would pose a threat to a potential organ recipient. Some quantitative NAT assays report the number of cycles until positivity (cycle threshold value) as a measure of viral particles present in the sample. Lower cycle threshold values correlate with more virus, and greater likelihood of recovering viable virus. Transmission risk is lower with high cycle threshold value infections [22]. However, no cycle threshold value is sufficiently reliable to distinguish an infectious from a non-infectious donor, and therefore decisions based on cycle threshold values are not currently recommended.

COVID-19 in solid organ transplantation candidates

Lung transplantation

There is limited but steadily increasing experience with lung transplantation for end-stage lung disease resulting from adult respiratory distress syndrome (ARDS)

secondary to SARS-CoV-2 infection. More than 35 cases have been reported in the literature to date [23-37]. Short-term mortality rates of approximately 10% to 15% were observed in these case reports, with variable follow-up duration. In most cases, more than 4-6 weeks had passed from initial COVID-19 diagnosis until transplant, and in the great majority of reported cases, SARS-CoV-2 PCR testing was negative prior to transplantation. A notable exception is a patient transplanted in Austria 8 weeks after COVID-19 diagnosis; SARS-CoV-2 PCR testing remained positive throughout transplant up to 10 days after transplantation. A Vero cell viral culture was performed that showed no viral growth prior to transplantation. The patient had a prolonged ICU stay of 63 days after transplant but was doing well at 144 days after transplantation [33]. Combined, these case reports support lung transplantation as a treatment option for end-stage lung disease after COVID-19 in highly selected patients. Selection criteria have been previously suggested and will continue to evolve as longer-term outcomes of these patients are reported [32, 38]. A duration of at least 4-6 weeks from COVID-19 diagnosis to listing for transplantation is reasonable in most cases to document lack of reversibility as well as to decrease the likelihood of ongoing viral replication. Whether negative results from SARS-CoV-2 PCR testing are required prior to lung transplantation, and how often and from what anatomical sources the samples for these tests should be obtained remain an unanswered questions. Other largely unanswered questions involve the longer-term impact of anti-inflammatory treatment given during the course of ARDS secondary to COVID-19, including long-acting IL-6 blockade.

Non-lung transplantation

Transplantation of non-lung organs into recipients with active symptomatic SARS-CoV-2 infection should be avoided given the associated proinflammatory state, the risk for respiratory failure, and risk for worsening infection after induction immunosuppression. A more common scenario is the recipient with asymptomatic SARS-CoV-2 infection, which is incidentally found on pre-transplant testing. In a recently reported survey of 92 US transplant centers, most centers would delay transplant in the setting of a positive SARS-CoV-2 PCR from a nasal swab in an asymptomatic kidney transplant candidate [19]. In 4% of surveyed centers, transplant could proceed as planned, if adjunctive testing such as imaging and/or antibody testing was reassuring. In a report on liver transplant in SARS-CoV-2 PCR-positivity around transplant, four candidates were successfully transplanted after incidental finding of SARS-CoV-2 PCR positive testing [39]. In these four patients, transplantation was postponed at least two weeks. One of these four patients developed a biliary leak and died of sepsis on day 24 after transplantation. Deceased donor liver transplantation from a SARS-CoV-2 PCR-positive donor to a SARS-CoV-2 PCR-positive recipient has also been reported [40]. In this case, transplant was delayed by 30 days after first positive PCR test in the intended recipient. The recipient remained PCR-positive on the day of transplant through day 24 after transplantation, and had a good outcome reported at 2 months follow-up. In summary, data on incidental PCR-positivity in transplant candidates are limited, with most centers favoring delaying transplantation and repeat testing. Data from non-transplant general surgery suggest that perioperative risk returns to baseline around 6 weeks after COVID-19 diagnosis [41]. However, delaying transplant may also be

associated with risk, and the decision on timing of transplantation after a COVID-19 positive test should be individualized.

COVID-19 after solid organ transplantation

Epidemiology and clinical features

Although the underlying immunocompromised state expectedly increases risk of infections in SOT recipients, many SOT recipients have adopted risk-reducing behaviors that may counteract risk of acquiring respiratory viral infections. Regional databases indicate that risk of community-acquired SARS-CoV-2 infection in solid organ transplant recipients is similar to risk in the general population. Heart and/or kidney transplant recipients may have greater risk of infection, though prevalence of infection between organ-specific groups is generally proportional to organ-specific recipient population [42, 43]. Risk factors such as age and underlying co-morbidities are better determinants of disease severity in SOT recipients than transplant-specific related factors including organ-type, maintenance immunosuppression, and timing since transplantation [44]. As with other infections, SOT recipients are less likely to have fever upon initial presentation with COVID-19. In contrast shortness of breath, more severe symptomatology, and development of renal failure are more common in SOT recipients [42, 45-47].

Short- and long-term outcomes

Despite initial reports suggesting that SOT recipients with severe COVID-19 were at greater risk of in-hospital mortality, in multiple subsequent studies – including

propensity-score analyses – similar survival to the general population has been observed [46-52]. However, SOT recipients are more likely to receive multiple COVID-19 directed therapies, including remdesivir, convalescent plasma, dexamethasone, and anti-IL6 antibodies [51]. Complications include bacterial and fungal superinfections, although corticosteroid and anti-IL6 antibody treatment are the best described risk factors for COVID-19 associated pulmonary aspergillosis, rather than SOT status [53]. In the United States, mortality in SOT recipients without critical illness also decreased in the later months of 2020 compared with earlier months of the pandemic [54]. Decreasing mortality trends were coincident with greater use of corticosteroids, remdesivir and convalescent plasma, and less use of anti-IL-6 agents, hydroxychloroquine, and fewer dose adjustments in calcineurin inhibitors [52, 54, 55]. The more prolonged duration of viral shedding in immunocompromised hosts has implications for both the individual and the community. Shedding not infrequently extends beyond 21 days, and has been reported to >250 days with prolonged illnesses, repeated relapses, and culture-recoverable virus all indicate the presence of ongoing viral replication and its consequences on the host [56-59]. Examples of multi-mutational SARS-CoV-2 variants arising in the setting of partial immune control in immunocompromised hosts raise concerns that such persistent infections could fuel the emergence of immune escape variants capable of spreading throughout even highly vaccinated populations [60].

Management of immunosuppression

Allograft dysfunction is a recognized consequence of many infectious diseases in SOT recipients. Thus, decisions to continue or withdraw anti-rejection immunosuppression need to balance the risk of progressive viral replication with the consequences of increasing the risk of developing rejection. The specific risk of allograft dysfunction occurrence and severity is poorly defined in SOT recipients with COVID-19. The use of antiproliferative agents such as mycophenolate mofetil has been linked to poor outcomes after COVID-19 in SOT recipients [61]. However, whether stopping antiproliferative agents during SARS-CoV-2 infection improves outcomes remains unclear. A small meta-analysis of 202 SOT recipients suggested no benefit of changing immunosuppressants [62]. In some cohorts, improved survival was seen among those who continued calcineurin-inhibitor during infection compared to those in whom calcineurin-inhibitor was stopped [62, 63]. Some have postulated that the immune suppression from anti-rejection medications may act to lessen the severity of the hyper-inflammatory stage of COVID-19. To this end, SOT recipients admitted with COVID-19 may have less need to escalate oxygen support compared with the general population [64]. However, SOT recipients have also been reported to generate higher levels of inflammatory markers (such as LDH, CRP, and ferritin) and have increased risk for bacterial and/or fungal superinfection [47]. In summary, data on impact of anti-rejection medication on COVID-19 outcomes are mixed, and decisions on whether to continue, dose-decrease, or stop specific anti-rejection medications in SOT recipients with symptomatic COVID-19 have not been standardized and treatment decisions are typically made for each individual case.

Prevention

Non-pharmacological interventions such as face coverings and physical distancing apply broadly to both immunocompetent and immunocompromised individuals [65]. Studies of natural infection suggest that despite more dramatic T and B cell lymphopenia during acute moderate/severe infection in SOT recipients, most SOT recipients eventually achieve functional immune responses comparable to the general population [66-68]. Neutralizing antibody level is the current best surrogate of immunological protection after vaccination [69]. Immune responses to vaccination, however, are highly variable and significantly diminished in immunocompromised hosts. As with other non-live attenuated vaccines, all currently available COVID-19 vaccines have a highly favorable safety profile in SOT recipients [70]. However, in contrast to the nearly universal serological response to mRNA-based COVID-19 vaccines in randomized control trials and real-world immunocompetent populations, less than half of SOT recipients may develop detectable anti-SARS-CoV-2 antibodies following a complete 2-shot series [70-73]. Older age, more recent transplantation, and use of an antimetabolite as immunosuppression associate with lower serological response, whereas liver recipient and vaccination with mRNA-1273 associate with greater serological response [72]. A third dose of mRNA-based vaccine within 3-4 weeks from dose two increases anti-SARS-CoV-2 antibody prevalence to 60-70% and enhances the magnitude of neutralizing antibody titer among responders [73-76]. As in the general population, prior infection with SARS-COV-2 also predicts greater response to mRNA-vaccines, including to the first dose [77]. In limited comparison studies, the serological response to mRNA-based vaccines in SOT recipients is greater than adenovirus-type

vector vaccines [78]. Thus, a 3-shot primary series of mRNA-based vaccines is currently preferred for SOT recipients. In a small series, a fourth dose further enhanced antibody and cellular responses in SOT recipients with a weak response after three mRNA vaccine doses [79].

Despite diminished antibody-responses observed in SOT recipients as compared to the general population, observational studies have estimated a 80% reduction in the incidence in COVID-19 in vaccinated SOT recipients compared with SOT recipients who are not vaccinated [80]. It is unclear whether these data indicate that stimulation of unmeasured non-B cell immunity provides protection, or if confounders such as coupling of vaccination with greater adherence to non-pharmaceutical risk reducing behaviors and/or greater likelihood of other household members also being vaccinated contributes to the risk reduction. COVID-19 mRNA-based vaccines do stimulate T-cell mediated cellular immune responses, even among patients receiving B-cell depleting therapies [81]. In SOT recipients receiving less potent, but more broadly compromising, immunosuppression, qualitative and quantitative T cell-mediated immune responses correlate with B cell responses, suggesting that even repeated vaccination may have only an incremental effect on vaccine-induced immunological protection in these hosts [75, 82, 83]. It is unclear whether heterologous boosting strategies (mixing), or antigen-based rather than intracellular vaccine products would result in augmented serological response in SOT recipients. Further studies contrasting natural infection-induced immunity with vaccine-derived immunity in SOT recipients may also help to inform vaccination strategies.

CONCLUSIONS

COVID-19 directed prevention and care of pre-transplant candidates and transplant organ recipients has rapidly evolved at both the individual and programmatic levels. Rapid infrastructure and donor-screening adaptations have paved the way for continuation of life-saving organ transplants, including the increasing need to perform lung transplantation for chronic sequelae of COVID-19. Recognition that the primary drivers of poor outcomes in SOT recipients are similar to those in the general population empowers providers to focus attention on optimizing management of patient co-morbidities while continuing immunosuppressants. As we enter the next phase of a pandemic in partially vaccinated populations, increasing attention is needed to understand the limits of immune control in SOT recipients, the potential consequences of persistent infections in SOT recipients leading to immune-escape variants, and the individual and population-level benefits of passive immune therapeutic strategies as prophylaxis for individuals with poor vaccine response.

Transparency declaration

Conflict of interest: **L.A.B.** receives royalties from *UpToDate®.* L.A.B. reports grants from NIH, outside the submitted work. **D.v.D.** is a consultant for Actavis, Tetraphase, Sanofi-Pasteur, MedImmune, Astellas, Merck, Allergan, T2Biosystems, Roche, Achaogen, Neumedicine, Shionogi, Pfizer, Entasis, QPex, Wellspring, Karius, and Utility. D.v.D. receives an editor's stipend from BSAC. D.v.D. reports grants from NIH, outside the submitted work.

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