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EDITORIAL

Respiratory viral infections in solid organ transplant recipients: New insights from multicenter data

Respiratory virus infections (RVIs), a persistent source of morbidity and mortality for solid organ transplant (SOT) recipients, have been best characterized in lung transplant recipients, in whom association with chronic lung allograft dysfunction has been reported.[1] However, much less is known about clinical presentations and outcomes of RVIs in non–lung transplant SOT recipients.

The Swiss Transplant Cohort Study represents a remarkable accomplishment, involving detailed, prospective data collection on most solid organ transplants performed at Swiss transplant centers. In the study by Mombelli et al, 696 RVIs were diagnosed in 3294 SOT recipients, with median follow-up of 3.4 years.[2] Cumulative incidence of RVIs was 60% in lung and 12% in nonlung recipients. RVIs were asymptomatic in 13.3% of lung and 2.6% of nonlung SOT. Hospitalization was required in 34.2%, and ICU admission in 3.9%; 30-day mortality was 0.18%. Bacterial coinfections occurred in 7.2% (and were associated with ICU admission) and fungal coinfections occurred in 3.4%. Use of oral ribavirin was uncommon in nonlung SOT recipients. Overall, RVIs were associated with graft loss or death in nonlung (but not lung) transplant recipients, but lower respiratory tract infections, and any occurrence of influenza, were associated with graft loss or death in both groups.

These interesting results raise many questions. First, the difference in asymptomatic infections between lung and nonlung recipients may reflect different testing thresholds, and detection of RVIs during surveillance bronchoscopies. Testing of an asymptomatic nonlung SOT recipient would be unlikely outside of a clinical trial; thus, the incidence of asymptomatic infection in the nonlung SOT group remains unclear. Another question relates to pathogenicity of different viruses. Interpretation of qualitative PCR results for detection of viral genome in multiplex respiratory samples is challenging, as there is no quantitation, and no distinction between replicative virus and nonreplicative virus or viral genome. Detection of viral genome might in one case indicate disease, or might be a bystander in another. Picornaviruses (mainly rhinoviruses) and seasonal coronaviruses (HCoV) accounted for 70% of asymptomatic RVIs in lung recipients, indicating a lower potential to cause disease, whereas influenza, respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), and human metapneumovirus (HMPV) were more likely to be symptomatic, and to require hospitalization.

What interventions should these results lead us to implement? Treatment seems to be of limited effect (although use of oral ribavirin in nonlung recipients was uncommon). Thus, prevention may have a more prominent role. Since influenza was a major factor in morbidity and mortality, influenza vaccination will be key. Protection might by optimized by using a more potent vaccine (e.g., high-dose,[3] adjuvanted, recombinant, cell culture based). In addition, prophylactic measures during the COVID-19 pandemic, such as universal masking and physical distancing, have been associated with a striking reduction in influenza, particularly in the Southern hemisphere.[4] Although the benefit of antiviral treatment for influenza was not clear in this cohort, it might be considered as preexposure prophylaxis in patients at special risk, if vaccine protection is insufficient.

This study not only focused on viral infections, but also reported bacterial and fungal coinfections. The role of these different infectious agents is difficult to analyze, in terms of relative contributions to disease severity. Which is the main cause and which is the innocent bystander, or are both influencing disease? Not surprisingly, bacterial infections were found to a high extent in patients in the ICU. Thus, managing coinfections might be of major importance.

The authors classified about 7% of infections as nosocomial, pointing to a need for special protective measures in the hospital, but this might be overestimated. They employed a widely used definition based on the onset of disease/detection 3 days or more after admission. This definition is appropriate for bacterial infections, but might be less useful for noninfluenza viruses such as RSV, HPIV, or HMPV, which have incubation periods of up to a week (although the median day of onset was 12.5 days after admission). Thus, the role of nosocomial infections may merit further study.

There are many questions for future research, including whether outcomes short of graft failure or death (e.g., allograft dysfunction) were associated with RVIs. It would also be of interest to know whether sequential occurrence of more than one RVI episode was associated with worse outcomes than a single episode. As the authors suggest, it will be important to track the impact of the COVID-19 pandemic on the incidence of other RVIs. Using protective measures for COVID-19 (in the community and in the hospital) might be adopted as a new standard, even after the pandemic.

In summary, the Swiss Transplant Cohort Study has made a valuable contribution to our understanding of respiratory viral infections in both lung and nonlung SOT recipients, through their database incorporating detailed infection-related data, and use of standardized

infection definitions. Although questions remain, we are indebted to these investigators for establishing this platform, which is poised to address many issues regarding infections in SOT recipients.

KEYWORDS

clinical research / practice, infection and infectious agents, infection and infectious agents - viral, infection and infectious agents - viral: influenza, infectious disease

DISCLOSURE

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