



Antifungal Prophylaxis

To the Editor:

Pennington and colleagues' study (1) supports administering antifungal prophylaxis to lung transplant recipients, as they found an approximately 50% reduction in all-cause mortality in those receiving prophylaxis. Yet they did not find a statistically significant reduction of invasive fungal infections. This could be due to insufficient statistical power but raises the possibility that the reduction of noninvasive fungal infections contributes to improved mortality. The authors stated that they were not able to evaluate the subsets of those who may derive a greater benefit from antifungal prophylaxis, such as patients with fungal airway colonization, high-risk occupations, or certain pretransplant diagnoses.

Our retrospective study of *Candida* in pulmonary secretions (2) found that among 82 inpatients and 11 outpatients referred for pulmonary consultation and followed for up to 5 years, *Candida* was likely clinically significant in 61%. Of the inpatients, death (or probable death) occurred in 43 (63%), 42 (98%) of whom died of definite or probable respiratory failure, with 13 (31%) deaths likely being related to mucus plugging, 16 (38%) deaths possibly resulting from mucus plugging, 6 (14%) deaths resulting from unknown causes, and 7 (17%) deaths not resulting from mucus plugging.

It is possible some of the mortality benefit from antifungal prophylaxis is due to preventing noninvasive fungal pulmonary disease,

including *Candida*-associated pulmonary disease. It would be interesting to know how many lung transplant deaths occur in patients with mucus plugging, atelectasis, and *Candida* in their pulmonary secretions. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

- 1 Pennington KM, Dykhoff HJ, Yao X, Sangaralingham LR, Shah ND, Peters SG, *et al*. The impact of antifungal prophylaxis in lung transplant recipients. *Ann Am Thorac Soc* 2021;18:468–476.
- 2 Johnson DC, Chirumamilla SK, Paez AP. Respiratory *Candida* in patients with bronchitis, mucus plugging, and atelectasis. *Open Respir Med J* 2020;14:87–92.

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Reply: Antifungal Prophylaxis

From the Authors:

In our published study (1), we found a reduction in all-cause mortality in lung transplant recipients who were receiving systemic antifungal prophylaxis compared with those who were not. Although the cumulative incidence of invasive fungal disease was lower in patients who were receiving antifungal prophylaxis compared with those who were not, this difference did not reach statistical significance. Johnson and Paez cite their prior work (2) on *Candida* spp. respiratory tract colonization resulting in mucous plugging, respiratory failure, and death as a possible explanation for our observation. Although this is an interesting point, it is difficult to attribute the difference in mortality in our study (1) to the prevention of *Candida* spp. respiratory tract colonization in patients receiving antifungal prophylaxis. As has been debated in the critical care and infectious disease literature for decades, it remains unclear whether *Candida* spp. airway colonization is a true causality for worse outcomes or is rather a marker of illness severity. Furthermore, it is unclear whether antifungal medications are effective at respiratory tract decontamination or preventing respiratory tract colonization particularly in lung transplant

recipients who have reduced blood supply at the airway anastomoses. Although *Candida* spp. airway colonization is relatively common in non-lung transplant critically ill patients, the incidence, impact, and natural history of *Candida* spp. airway colonization has not been described in the lung transplant population.

Baker and colleagues (3), in the largest study on post-lung transplant fungal epidemiology, reported the prevalence of invasive *Candida* infections in lung transplant recipients to be 11.4% in the setting of universal inhaled amphotericin B combined with a targeted preemptive systemic antifungal prophylactic strategy. Bloodstream, pleural space, and surgical site infections, but not respiratory tract or lung parenchymal pathology, were the dominant types of invasive *Candida* infection. Interestingly, about 20% of invasive *Candida* infections occurred while patients were receiving systemic antifungal prophylaxis. The low prevalence of respiratory system-related *Candida* disease and the incidence of breakthrough *Candida* infections while receiving systemic antifungal prophylaxis does cast doubt that *Candida* airway colonization could be a significant contributor to mortality in our study cohort.