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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Author Contributions: D.C.J. did first draft of letter and A.P.P. helped revise the letter, and both contributed to intellectual content and final approval.

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*

Author Contributions: K.M.P. wrote the first draft of letter. R.R.R. and C.C.K. provided critical revisions. All authors contributed to intellectual content and approval of the final version to be published.

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.

Although the difference in the incidence of invasive fungal disease did not reach statistical significance in our study (1), it is still likely that the reduction in observed mortality is partly secondary to a reduction in the incidence of invasive fungal disease. Mortality is an absolute outcome. Invasive fungal disease as an outcome requires achieving the correct diagnosis and then billing the most appropriate diagnostic code. Further randomized, prospective studies are needed to fully delineate the risks and benefits of universal, systemic antifungal medications for lung transplant recipients. ■

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Adoption of Antifibrotic Medications: A Closer Look at the Data

To the Editor:

We read with great interest the paper by Dempsey and colleagues entitled "Adoption of the Anti-Fibrotic Medications Pirfenidone and Nintedanib for Patients with Idiopathic Pulmonary Fibrosis" (1). This is an area of great importance as we seek to better understand the uptake of novel therapeutics within the United States in a disease in which no prior approved therapies were available. Understanding adoption rates of such therapies helps to inform researchers in academic settings, clinical practice, and industry as we attempt to improve the lives of our patients with these diseases.

In this article, the authors demonstrate a relatively low rate of antifibrotic medication adoption since it was first approved in the United States for idiopathic pulmonary fibrosis (IPF) in 2014. We have no reason to doubt the veracity of the data but suggest that the time interval examined underestimates the true rate of adoption of these therapeutic agents. Per Rogers' diffusion of innovation theory (2), adoption of innovation is a process that occurs over time as more people are willing to do something they had not done previously. In the current study, the authors identified an adoption rate of both nintedanib and pirfenidone of approximately 13.2% each, which is reported as the average adoption rate over the study period (October 1, 2014, to July 31, 2019). However, a closer look at the data by our team suggests a different pattern. Using the same OptumLabs data of commercial and Medicare Advantage members with IPF, we indeed found a similar adoption rate of nintedanib as reported by Dempsey and colleagues (1). However, breaking down the observed time period into annual calendar year intervals, we observed a different trend. In fact, we found that the proportion of patients being treated with antifibrotic therapy ranges from 2.6% (for the 3 months encompassing October–December 2014) to 36.8% (for the first 6 months of 2019), and we believe this provides a more representative picture of antifibrotic adoption as well as the trend.

The reason(s) for the early slower uptake are unclear. One factor of potential importance is patient access to pulmonologists. Approximately half of the untreated patients with IPF in this data set had a visit to a pulmonologist during the baseline period, whereas this rate was significantly higher for treated patients (76%). For IPF, which is primarily specialist managed, access to a pulmonary specialist likely regulates the implementation of a new IPF treatment. Whether this is due to geographical limitations, insurance benefits, or other contributing factors is unknown, but it also likely contributes to the discrepancy in adoption of antifibrotics the authors noted.

We urge the authors to reconsider their results in light of these points, as it may result in drawing more comprehensive conclusions about the findings. We also note that both antifibrotics are accompanied by robust patient-assistance programs, which mitigate the out-of-pocket costs to many patients unable to afford them; thus, the conclusion that low adoption of antifibrotics "may be associated with the high out-of-pocket cost" appears premature and perhaps incomplete. ■

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

Supported by Boehringer Ingelheim. All authors are employees of Boehringer Ingelheim Pharmaceuticals, Inc.