or by failure to account for differing wait times before the onset of treatment. In the case of our nested case-control analysis, which is not subject to immortal time bias, Suissa is concerned about an information bias. He suggests that patients with COPD who died might have had earlier hospitalizations during which ICS were prescribed unknown to their general practitioners (GPs). However, in Methods, we explained how we designed our analysis to avoid this possibility. To enter the nested case-control study, the patient had to have a first COPD-related hospitalization. The period subsequently analyzed for treatment was drawn from between 30 and 365 days after discharge when the patient was under the clinical care of the GP. If the patient was rehospitalized within these 365 days, the retrospective analysis started from the index day of readmission. To allow for cases in which duration between discharge and index days was less than 6 months, control subjects were matched for duration of follow-up of each such case. Indeed, we defined an outcome event as the first occurrence of either COPD-related rehospitalization or death. Hence, no adjustment is required to our published data.

Our second analysis, using propensity scores to improve matching of baseline characteristics, is, as stated in our article, subject to wait time bias, which we sought to avoid by ensuring both groups were determined on the day of discharge. Because of the great difficulty in handling data from patients in whom treatment was switched during the period of follow-up, inevitably we had to take a “peek into the future.” Indeed, our ability to construct the whole cohort of patients for subsequent analysis by both methods requires that we know that suitable records exist for 1 year of follow-up or until an earlier outcome. Regarding our propensity scores–based analysis, Suissa’s recommendation ignored the reasons we gave against an application of what was essentially the “treatment switching” methodology. As referenced in our article, standard texts and publications on biostatistics and epidemiology have warned against use of this methodology unless the strong assumption on which it is based can be satisfied—namely, that the reason for the change of exposure status is unrelated to the risk of subsequent event (2–5). For our study, this translates to an assumption that the reason why a GP subsequently prescribed ICS to a patient for the first time was unrelated to the patient’s disease severity status—an assumption that clearly violates both existing guidelines (6) and the regular judgment involved in clinical practice. This problem cannot be avoided by censoring patients at first exposure to ICS as Suissa suggests, since such censoring will be informative to the risk of an event, making the analysis still inappropriate. We note that Suissa has not offered any explanation on how his recommended approach satisfied this fundamental assumption.

The problem of confounding by indication was more influential than immortal time bias in our data. Consequently, adoption of Suissa’s suggestion would result in both ignoring the confounding bias and incorrectly accounting for the much smaller immortal time bias. Not surprisingly, Suissa’s calculation indicated ICS as possibly associated with an elevation of risk of COPD hospitalization or death. If ICS were not effective, an association should be absent even if exposed patients were only compared with the subpopulation of patients who were never exposed to ICS. In our article, we went further to address this issue of exposure misclassification and confounding by severity by restricting our comparison to exposed patients with the same propensity for ICS prescription as unexposed patients at time of discharge to reduce the more influential bias due to absence of randomization.

We do, however, agree with Samet that, while the contributions of observational data are important, more definitive conclusions can be drawn from controlled trials (7).
article by Yates and colleagues reports the experience with a select cohort of 20 patients at a large transplant center (2). The authors conclude that azithromycin reverses airflow obstruction in patients with BOS. The data presented in this article raise important questions about this therapy, and we echo the authors’ caution that this therapy should not be viewed as a panacea for the treatment of BOS.

Yates and coworkers report their results for FEV1 as a percentage of change from baseline. Although these changes appear dramatic in Figure 1 of the article, they do not necessarily reflect a clinical benefit for these patients. The mean FEV1 before initiation of therapy was 1.44 L (range, 0.54–3.28) and the mean improvement was 0.11 L (range, –0.07 to 0.73). This mean improvement represents an increase in FEV1 of 8% for the overall group. The results were reported after 3 months; however, by 6 months, 8 of 20 patients (40%) had no improvement (5 who had experienced initial improvement no longer sustained this improvement, and 3 patients did not experience improvement). Finally, the follow-up period was relatively short. Nevertheless, it is important to acknowledge that in the article by Yates and coworkers (2) as well as the original publication by Gerhardt and coworkers (1), there were some patients with BOS treated with azithromycin who did experience a significant improvement in pulmonary function. The objective, as mentioned in the accompanying editorial by Drs. Williams and Verleden, should be to conduct a large clinical trial with long-term follow-up to determine which patients might benefit from this therapy (3).

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References


From the Authors:

Since our initial observation of significant and occasionally dramatic reversal of airflow obstruction in bronchiolitis obliterans syndrome (BOS) (1), other groups have described their experience with this novel therapeutic approach for this most devastating long-term complication of lung transplantation (2–4). Verleden and Dupont (2) and, more recently, Yates and colleagues (3) observed a favorable response to azithromycin in a sizable proportion of their respective series. The letter from Dr. Angel and colleagues questions the clinical significance of the improvement in airflow obstruction documented by Yates and coworkers. They also describe their own experience showing little long-term improvement for a small cohort of patients treated at their institution, mirroring the disappointing results by Shitrit and coworkers (4). Clearly, the response to azithromycin is quite variable, which is not unexpected, given the likely heterogeneous nature of the factors involved in the pathogenesis of this clinical syndrome. Perhaps those patients with active airway inflammation or bronchoalveolar lavage neutrophilia and/or elevated interleukin-8 concentrations are more apt to respond (5).

We wholeheartedly agree with Dr. Angel and colleagues and Drs. Williams and Verleden (5) that a carefully designed, prospective, multicenter, randomized trial of azithromycin is needed urgently to determine conclusively whether this therapy is of benefit and to identify which patients are likely to respond. Given the lack of enthusiasm on the part of the pharmaceutical industry to support such a trial for a disease affecting a small patient population, alternative funding will be required. Recently, the National Institutes of Health convened a workshop on lung transplantation, with the expert panel concluding that multicenter studies were imperative (6). We believe the time has come to form a network of lung transplant centers to study important questions in lung transplantation, so as to move the field forward toward improved transplant outcomes and patient survival. We call on the National Institutes of Health to support such an initiative as suggested by the expert panel.

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LUNG TRANSPLANTATION: OPPORTUNITIES FOR RESEARCH AND CLINICAL ADVANCEMENT

To the Editor:

We read with great interest the article by Wilkes and colleagues that summarized the scientific and clinical advancements in lung transplantation (1). We would like to expand on the advancements that have been made in the area of humoral rejection. Wilkes and coworkers describe the association of soluble C4d in bronchoalveolar lavage fluid and the presence of anti-HLA antibodies. In their study, a definitive correlation between C4d...