Response

To the Editor:

We thank Dr Mao and colleagues for their insightful comments and the opportunity to clarify a number of points from our work.1 Although we considered inclusion of additional risk variables into the latent class analysis model,1 we chose to use time changes in primary graft dysfunction (PGD) grade only to derive our classes for several reasons. First, we sought to address controversy surrounding PGD phenotypes encompassed within the International Society for Heart & Lung Transplantation definition based on timing of clinical PGD development.2-3 Second, we did not have a large enough sample size to include all known risk factors for PGD in the model and generate stable classes. Third, using grade alone to derive the classes allowed us to demonstrate construct validity of the resultant PGD phenotypes using many of the known clinical risk factors for PGD and mortality.

We have previously published on clinical risk factors in PGD.4 In the current study, we evaluated which of these many risk factors would distinguish between the classes. We agree that recipient BMI, for example, remains an important risk factor for PGD; however, differences in BMI did not help distinguish between those patients who will recover from injury quickly and those with persistent injury. The factors we identified, including volume of blood transfusion and cardiopulmonary bypass use, may be helpful in identifying those who are at risk for graft dysfunction persisting on day 3 as well as identifying potential mechanistic links to the persistent PGD phenotype.

In the Lung Transplant Outcomes Group cohort study, subjects receiving extracorporeal membrane oxygenation (ECMO) for graft dysfunction are classified as having grade 3 PGD. Therefore, we do not believe the use of ECMO in this study created a misclassification bias by making it appear that subjects recovered from PGD when they did not. Additionally, only one subject in this cohort was on ECMO 72 h after transplantation, so we do not think there was significant contribution from the use of ECMO.

Although our analyses generated classes that differed in time of resolution, we did include all subjects with grade 3 PGD at any time. The latent class model best defined classes based on resolution of lung injury, but classes based on development of injury were less apparent. However, had a class of late-onset injury been common, we believe our model would have identified this pattern. We limited our study to PGD within 72 h, as that is the commonly accepted definition,2 although certainly lung injury can occur at later time points.

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REFERENCES


N-Acetylcysteine Protection in COPD
An Alternative Mechanism of Action

To the Editor:

We read with interest the study by Tse et al1 in a recent issue of CHEST (July 2013). In their study, 1-year treatment with highdose N-acetylcysteine (NAC) resulted in improved small airway function and decreased exacerbation frequency in patients with COPD. The authors proposed that the reduction in COPD exacerbations might be related to antioxidant and antiinflammatory effects of NAC, resulting in improved small airway function in COPD. Additionally, they proposed that NAC might reduce exacerbations by inhibiting bacterial adherence to ciliated epithelial cells and by NAC mucolytic effects.

Although we agree with these possibilities, one additional mechanism was not discussed. We propose that a major mechanism of
NAC-mediated prevention of COPD exacerbations is through restoration of the normal antiviral innate immune response that is suppressed by cigarette smoking and perhaps in COPD. Cigarette smoking is the major cause of COPD and predisposes patients to severe respiratory tract infections. Respiratory viral infections with rhinoviruses, influenza viruses, and respiratory syncytial virus are the main causes of COPD exacerbations, which are associated with disease progression and loss of lung function. Specifically, several studies have confirmed the relationship between cigarette smoking and the risk of influenza infection. Influenza infections are more severe, with more cough, acute and chronic phlegm production, breathlessness, and wheezing in smokers. The mechanism of increased susceptibility to infections in smokers is likely multifactorial but clearly includes an alteration of immunologic host defenses.

We have demonstrated that cigarette smoke extract (CSE) suppresses host antiviral activity in a human lung model. Thus, cigarette smoke exacerbates the susceptibility of the host to respiratory infectious diseases and the attendant pathology. We found that CSE treatment inhibited influenza-induced antiviral cytokine expression in our human model. This is associated with CSE-inhibited messenger RNA and protein expression of the major RNA virus sentinel RIG-I that is important in the antiviral host response. However, inhibition of viral-mediated RIG-I induction by CSE was prevented, and antiviral cytokine responses were restored by NAC. The interactions between host immune responses and influenza virus usually determine the outcome of infection. Restoration of these responses by NAC may have been a major mechanism in the decrease in exacerbations demonstrated by Tse et al in patients with COPD.

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Response

To the Editor:

We would like to thank Dr Wu and colleagues for their response to our article1 and for raising the question about alternate mechanisms explaining the action of N-acetylcysteine (NAC) in reducing COPD exacerbations. In a human lung model2 NAC could restore the antiviral cytokine response and prevent the inhibitory effect of cigarette smoke extract (CSE) on the viral-mediated retinoic acid-inducible gene (RIG-I), which is an important pattern recognition receptor that senses influenza. This dose-dependent effect of NAC on the innate immune response further supported the use of higher-dose NAC in the treatment of patients with chronic COPD, as shown in our previous The Effect of High Dose N-acetylcysteine on Air Trapping and Airway Resistance of Chronic Obstructive Pulmonary Disease—a Double-Blinded, Randomized, Placebo-Controlled Trial (HIACE).3

We have reservations in concluding that its effect on the innate immune system is the major mechanism for reducing COPD exacerbations. First, influenza infection is not the sole cause of COPD exacerbations; in fact, other respiratory viruses (human rhinovirus, respiratory syncytial virus, human metapneumovirus, coronavirus, and adenoviruses) were recognized during exacerbations. The majority of our patients with COPD in the HIACE were ex-smokers; it is unknown whether cigarette smoking has a sustained long-term suppressive effect on the innate immune response. Moreover, at present, there are still limited clinical data in patients with COPD that demonstrate the interaction between cigarette smoking and NAC in “virus-induced exacerbation.” To extrapolate the in vivo results to patients with COPD, it seems that further clinical studies are warranted, especially to demonstrate the attenuated innate immune response in patients with COPD and the clinical effect of NAC in enhancing innate response as well as reducing virus-induced exacerbations in patients with COPD.

In fact, exacerbation of COPD is multifactorial. NAC may act on various target sites, resulting in the reduction of exacerbations. In addition to its mucolytic effect, antioxidant and antiinflammatory properties of NAC could attenuate the chronic airway inflammation as well as improve small airways function and reduce air trapping. For example, patients with COPD are characterized by overexpression of adhesion molecules (eg, intercellular adhesion molecule-1, which causes excessive transmigration of neutrophils). It was shown in an in vitro study4 that NAC could exert its antiinflammatory effect by inhibiting cytokines that stimulated IL-8 and intercellular adhesion molecule-1 in endothelial and epithelial cells. Other effects that were demonstrated by NAC include (1) reductions of lysozyme and lactoferrin concentrations in smokers, 5 (2) reduction in the activation and number of neutrophils and macrophages in BAL fluid in smokers,5 and (3) inhibition of the adherence of bacteria to ciliated epithelial cells in vitro.6 Nevertheless, the authors’ comments have definitely shed light on the potential mechanism for our previous observation that NAC could reduce exacerbation in patients with COPD. Further clinical studies are warranted to confirm the hypothesis.

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194