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Response to “Exploring causative pathology is essential for validating harmful effects of late intubation”

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We thank Drs. Kyo, Ohshimo and Shime (1) for their thoughtful insights on potential mechanisms of increased mortality in ARDS patients with late intubation. (2) The authors astutely point out several clinical factors that could potentially differentiate initially non-intubated patients with ARDS who went on to require late intubation from those who did not. Unfortunately, in this retrospective analysis of a prospective cohort, we do not have data on indications for intubation, severity of illness at the time of intubation, or detailed information on respiratory management between ARDS diagnosis and intubation. We agree with the authors that this kind of granular data could reveal important insights on the mechanisms of late intubation.

What our study demonstrates is that initially non-intubated patients who went on to require late intubation were similar at the time of ARDS diagnosis to those who never required intubation. This suggests that whatever changes occurred between these two groups occurred after ARDS diagnosis. These results highlight the importance of prospective evaluation of

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timing of intubation with detailed collection of measures of respiratory and hemodynamic parameters during the time leading up to intubation.

In addition, the authors raise the important issue of appropriate antibiotic therapy in critically-ill patients. While most of the patients in the cohort received antimicrobial therapy, we unfortunately do not have any data on the appropriateness of the therapy given. Furthermore, as is common, many critically-ill patients have negative culture data, so definitive evidence of inappropriate therapy, even in prospectively collected studies, is likely to be challenging. We agree that bronchoalveolar lavage (BAL) would provide additional microbial data; however, BAL was not routinely collected as part of this study.

Finally, the authors question the number of variables included in multivariate analysis to evaluate the adjusted association between timing of intubation (early, late and never) and mortality at 60 days. Based on the recommendation of a statistician prior to publication, we used backward selection to include only the most relevant variables in our model. We found 10 variables that met inclusion using the backward selection model, which was felt to be reasonable given the consistency of the direction of the association when each of the variables was independently adjusted. Furthermore, in the comparison of mortality between just the never intubated and late intubated patients, a propensity score created from the same variables found a similarly increased hazard ratio in adjusted analysis.

In summary, we appreciate the authors' suggestions and agree that validation of our results in a prospectively conducted study with detailed collection of data on hemodynamic and respiratory variables prior to intubation would be an appropriate next step to understanding the causes of adverse outcomes in patients who undergo late intubation.

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