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## Reply to Sklar and Yarnell and to Stahl *et al.*

*From the Authors*:

We thank Sklar and Yarnell and Stahl and colleagues for their interest in our study (1). In their comment, Sklar and Yarnell raise the methodological issue of selection bias in our cohort, and more specifically how excluding patients who never have the exposure of interest could affect the effect estimation of such exposure on the outcome. They correctly point out that the effect of late exposure to invasive mechanical ventilation is probably overestimated when patients who have never been intubated are excluded from the analysis. Thus, we fully agree that our findings cannot be understood as a comparison of early versus late intubation, as lack of patients without intubation in the "late group" might bias the denominator.

In addition, Stahl and colleagues point out the question of the causal pathway between initial oxygenation strategy, need for intubation, and outcome. In particular, they suggest a novel approach to avoid intubation in this population, namely awake extracorporeal membrane oxygenation (ECMO) strategy. Although authors have reported a feasibility study of this approach, its benefits especially when compared with usual oxygenation strategies remain to be demonstrated. Twenty years ago, Hilbert and colleagues in their landmark trial reported a significant reduction in intubation and mortality rates associated with noninvasive ventilation used in immunocompromised patients, an improvement partly ascribable to a high mortality rate when invasive mechanical ventilation was needed at this time (2). These results have been challenged by more recent trials (3, 4), but avoiding intubation in this population remains a major goal for several physicians (5). Our study aims to nuance this assertion. First, although mortality remained high in that setting, we observed a significant decrease in mortality rate when intubation is needed. Second, we observed that within the set of patients who required invasive mechanical ventilation, some had failed prolonged noninvasive oxygenation or ventilation challenge with higher subsequent mortality. These results are in line with the high reported mortality rate after "awake ECMO" failure, used to avoid mechanical ventilation at all costs. Third, this opens field to understand this excess mortality, which may be because of influence of a lack of improvement or deterioration in clinical status and of risk of cardiac arrest during intubation in the most hypoxemic patients (6).

Thus, from our point of view, our data should not be interpreted as an advocacy for an early or late ventilation strategy but as the evidence of a paradigm shift in respiratory failure management in immunocompromised patients: from "avoid intubation at all costs" to "intubate earlier those at high risk to require it," while offering a new research agenda: *1*) delineate, identify, and predict patients' ventilation strategy trajectory; *2*) develop and validate individualized oxygenation strategy; and *3*) include such strategy in a multimodal approach, including the optimal diagnostic strategy and ideal prevention of ICU-acquired events while taking into account context and underlying immune defect. ■

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

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