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Staying Awake in Severe Acute Respiratory Distress Syndrome: A Perspective on Immunocompromised Patients

To the Editor:

We read with great interest the recent report in the *Journal* of Dumas and colleagues summarizing extensive data on ventilation strategies in immunocompromised patients with acute respiratory failure (ARF) (1). The authors concluded that delayed intubation might be independently associated with increased mortality in immunocompromised patients.

Pickkers and van Haren challenged this conclusion in their thoughtful editorial by emphasizing several important limitations of the study, including incomplete available data from all included studies and the overall small number of randomized studies conferring the risk of several confounding issues (2). The most important limitation is based on the fact that all noninvasively ventilated patients included in this meta-analysis were eventually intubated, not allowing any robust statements about inferiority of noninvasive techniques *per se*.

We agree with our colleagues that this introduces a strong selection bias, as patients who will eventually fail noninvasive ventilation (NIV) might differ in many characteristics from those that might be successfully bridged with an NIV strategy. Bearing in mind the exceedingly high mortality rate of immunocompromised patients requiring invasive mechanical ventilation (1), we believe it would be premature to advise toward a general rule of early intubation in all of these patients.

Ventilator-induced lung injury, ventilator-acquired pneumonia, and ventilator-induced diaphragm dysfunction are well-known side effects of invasive ventilation and may contribute to and aggravate the complex pathophysiology of multiorgan failure and death in ARF (3). The use of extracorporeal membrane oxygenation (ECMO) in nonintubated patients who are awake and spontaneously breathing (termed awake ECMO) might theoretically avoid side effects and complications associated with sedation, intubation, and invasive mechanical ventilation (4). We

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recently described our single-center experience with a primary awake ECMO strategy in 18 nonintubated immunocompromised patients with severe acute respiratory distress syndrome (median PaO₂/FiO₂, 72 [65–82]) who presented without secondary organ dysfunction (5). During their ICU stay, 11 patients (61%) required secondary intubation. Of note, the most common reason for secondary intubation was severe agitation. In-hospital mortality was 73% in patients who required secondary intubation versus 14% in patients who did not require intubation while on ECMO support (hazard ratio, 0.133 [0.058–0.789; P = 0.023]).

Although limited by the small sample size and the uncontrolled nature of the study, we believe that these data demonstrate as a proof of principle that in selected immunocompromised patients with acute respiratory distress syndrome, an awake ECMO strategy may be used to avoid intubation and mechanical ventilation. Of course, further data are needed, but the high mortality rate of immunocompromised patients who require mechanical ventilation warrants the exploration of alternative strategies.

A patient-individualized approach considering all available options and continuously weighing the benefits of avoiding the well-known side effects of invasive ventilation while not ignoring the risks of patient self-inflicted lung injury (6) provoked by delaying intubation for too long clearly will be critical on our path toward improving the care of immunocompromised patients with ARF. ■

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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 hypoxic 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. ■

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