



Always Say Never: Why Studies of Timing of Invasive Ventilation Should Compare “Early versus Late/ Never” as Opposed to “Early versus Late”

To the Editor:

The recent study by Dumas and colleagues makes a valuable contribution to the descriptive epidemiology of invasive ventilation in immunocompromised patients (1). However, the study results must be interpreted in the context of methodological bias, which may substantially interfere with inferences about the timing of invasive ventilation. It is not the usual issue of residual confounding that makes a mandatory appearance in the discussion section of all observational studies. Instead, this is an issue of cohort construction that makes inferences about the timing of invasive ventilation more difficult to interpret than might be perceived.

The issue is that the study only includes patients who were invasively ventilated. To see why this is a problem, consider a randomized trial of earlier versus later invasive ventilation. Some of the patients assigned to the “later” strategy would improve before the later time arrived and thereby avoid invasive ventilation altogether. We have seen this in other areas of critical care, such as renal replacement therapy. In the STAART-AKI (Standard vs. Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury) trial, for example, only 62% of patients assigned to the later dialysis strategy were ever started on renal replacement therapy (2). It would be an obvious error to exclude patients who were never dialyzed from the analysis of that study. Similarly, any causal inference about the timing of invasive ventilation requires including the outcomes of patients that were never invasively ventilated because a later strategy was used.

This methodological oversight is a recurring blind spot in the critical care literature (3–6), and each study has dutifully demonstrated the power of this error in construction. Investigators uniformly found higher mortality in the “late” intubation cohorts, which can likely be explained by the benefit of time in clarifying clinical trajectories as opposed to the benefit of early invasive ventilation. Early invasive ventilation will inevitably place some patients on ventilators who never would have been invasively ventilated under a later invasive ventilation strategy because time has not allowed those patients the chance to improve. Other studies have navigated this potential pitfall correctly and they show that mortality is lowest in patients who were never invasively ventilated (7–9). We wonder whether characterizing the invasive ventilation timing as “early versus late/never” instead of “early versus late” would help future authors avoid this cohort construction pitfall.

Invasive ventilation and the best way to deploy it is a key research priority for critical care medicine. We agree with the authors’

fundamental assertion that invasive ventilation has important heterogeneity of treatment effect. Unfortunately, the construction of this analysis precludes concrete inferences about this heterogeneity, including the relationship between timing of invasive ventilation and mortality. We encourage future studies of invasive ventilation to include all patients potentially eligible for invasive ventilation in their cohorts. Identification of the variables truly relevant to heterogeneity of treatment effect is the key step to enable a randomized controlled trial of invasive ventilation. We thank Dumas and colleagues for their manuscript and the opportunity it affords to discuss bias in studies of invasive ventilation. ■

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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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