Untangling Lower Airway Dysbiosis in Critically Ill Patients with COVID-19

For patients with coronavirus disease (COVID-19) that require management in an ICU, mortality varies between 30–70% and patients’ heterogeneity, few studies have focused on applying this to a cohort with similar disease severity (e.g., exclusively critically ill patients) and with longitudinal follow-up. Furthermore, most investigations have focused on noninvasive assessments, such as blood, to develop biomarkers that may predict disease outcome. Although that for sure would be quite convenient, the samples we really need to study are those collected from the primary site of the disease: the lung (7).

In this issue of the Journal, Kullberg and colleagues (pp. 846–856) studied how the lower airway microbiome on 114 critically ill, mechanically ventilated patients infected with SARS-CoV-2 can be associated with poor clinical outcome (8). In these patients, BAL samples were obtained after days or weeks from initial intubation (median time from intubation to sample collection was 9 d) and in 32 patients they were able to analyze follow-up samples. The authors evaluated for microbial signatures associated with successful liberation from mechanical ventilation by day 60 after intubation (versus deceased or intubated >60 d). To do that, the lower airway microbiota was characterized by 16S rRNA gene sequencing and bacterial and fungal load were measured by qPCR targeting the 16S and 18S rRNA genes, respectively. In line with a prior study of >140 critically ill patients with COVID-19 (9), poor clinical outcome was associated with higher bacterial load. Importantly, the authors showed that increased fungal load was also associated with poor clinical outcome. The authors also found that some inflammatory markers measured in these samples correlated with bacteria/fungal load, such as tumor necrosis factor α. Moreover, the study aimed to evaluate if secondary bacterial pneumonia, defined here as BAL culture positivity (which occurred in 22% of cases), was associated with changes in the microbiota. They found that BAL culture positivity was indeed associated with increased bacterial load and there was some concordance between the isolated bacterial strain...
and the increased relative abundance in the 16S rRNA gene sequencing data.

In the context of other investigations on lower airway samples from critically ill patients with COVID-19, these results solidify the notion that it is not just uncontrollable SARS-CoV-2 infection that kills patients with COVID-19, though that’s likely one big part of it. In a different study using metatranscriptomic and metagenomic approaches on bronchoalveolar samples from 142 critically ill patients, mortality was associated with increased lower airway viral load and a decrease in anti-SARS-CoV-2 specific IgG levels (9). However, the association of poor outcome with increased microbial load, other than SARS-CoV-2, was found in both studies supporting that other microbes may be contributing to the disease process. Alternatively, the dynamic change in microbes other than SARS-CoV-2 may uncover alterations in the host immune response and serve as biomarkers that may allow us to risk-stratify patients (Figure 1A).

The results of the paper now published in the Blue Journal highlights several challenges of conducting research in critically ill patients (Figure 1B). First, ideal biomarkers should be developed at early time points where interventions are more likely to affect the course of disease and should be able help us understand temporal changes in a patient’s conditions. In the current study, for the most part, samples were obtained on the second week of mechanical ventilation or after. Considering that, at the beginning of the pandemic, many professional societies recommended against performing bronchoscopic procedures in patients with COVID-19 under the concern for transmission to healthcare workers (10), having collected this many samples is already commendable. However, we need to do better. To
develop clinically usable biomarkers among critically ill patients, samples will need to be obtained at early time points, e.g., upon admission to the ICU or soon after intubation, and longitudinally. In the study of critically ill patients with SARS-CoV-2, another challenge is the correct selection of time-dependent outcomes as traditional “critical care outcomes” such as 28-day mortality or 28-day ventilator free days may not appropriately capture the complexity of clinical trajectories in this disease. As we learned in this pandemic, critically ill patients with COVID-19 commonly require lengthy mechanical ventilation and a large proportion of these patients will succumb way after the first month. This has led to the recommendation of 60 days from hospitalization as a landmark for evaluating mortality (11). To complicate things further, the time from a patient’s onset of symptoms to hospitalization, or from hospitalization to ICU admission (or intubation), can vary greatly. As shown in the current paper and others, individuals can spend only a few days to multiple weeks in the hospital before being admitted to the ICU (11). This discrepancy becomes particularly relevant when defining the outcome of interest, as one would hope that biomarkers predict outcome among patients with similar degree of severity (in this case, when respiratory failure is declared and intubation is needed) and with the time to outcome adjusted for when measurements are made. Here, the authors evaluated their biomarkers’ accuracy to predict 60-day extubation success (versus extubation failure or mortality) from intubation and, in secondary analyses, from sample collection. This highlights how establishing proper clinical outcomes for group comparisons remains a significant challenge. Another major challenge is being able to properly capture time-dependent confounders in these complex patients. One example is the use of antibiotics and immunosuppression, broadly used in this cohort and of particular interest given the effects on the lower airway microbiome. Although there has been some standardization in care provided to these patients since the start of the pandemic (take, for example, how steroid use has changed), the use of many forms of immunosuppression and antibiotics differ widely and require careful adjustment and, ideally, longitudinal investigations. For example, here the authors included antibiotic exposure as part of their model but we cannot evaluate the individual effect of different antibiotics. Finally, it is particularly challenging to identify secondary bacterial pneumonias in these critically ill patients in the setting of viral acute respiratory distress syndrome (12, 13). Although the authors here used BAL culture positivity to identify those with potential VAPs, an important next step is to use other clinical data available (e.g., worsening oxygenation, imaging) as well.

Bottom line, we need more studies including early time points, longitudinal samples, and detailed consideration of all possible confounders. Why? Disentangling this web of microbial, pathogen, and host dynamics is the only way we will be able to risk-stratify patients and identify treatable traits (14).

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