The Puzzles of Ventilator-Associated Pneumonia and COVID-19: Absolute Knowns and Relative Unknowns*

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The development of ventilator-associated pneumonia (VAP) (1) in ICU patients with severe COVID-19 is common and associated with higher VAP rates compared with non-COVID-19 patients in several retrospective studies (2–6). Additionally, there is an increased risk of shock and blood stream infections associated with VAP in COVID-19 (5).

A challenge in understanding the reason for this increased rate is the lack of a clear definition of VAP in COVID-19. Due to the frequent concomitant presence of fever, leukocytosis, and lung infiltrates due to the viral infection, differentiating bacterial colonization from a new bacterial secondary infection is challenging in the presence of these symptoms and imaging findings of an acute viral pneumonia. In part due to these challenges, the term ventilator-associated lower respiratory tract infection (VA-LRTI) has been used: the rate of VA-LRTI has also been found to be higher in ICU patients with COVID-19 compared with ICU patients with influenza and those without viral infection (7).

A key remaining question is why VAP and VA-LRTI occur at higher rates in COVID-19 patients. Proposed reasons for increased rate of VAP and VA-LRTI in COVID-19 include viral immunomodulation, prolonged mechanical ventilation and hospital stay, steroids use, acute respiratory distress syndrome (ARDS), prone positioning, sedating and neuromuscular blocking agents, vasopressor use, extracorporeal mechanical oxygenation utilization, and increased demands of the healthcare system including patient volume, healthcare worker shortages, and use of personal protective equipment (8). Prior studies have not systematically evaluated how VA-LRTI has changed throughout the pandemic.

In this issue of *Critical Care Medicine*, Hedberg et al (9) expand on the epidemiology of VA-LRTIs in COVID-19 using a retrospective analysis of ventilated adults in a large Swedish ICU from January 2011 to December 2020. Their primary goal was to evaluate changes in rate of VA-LRTI in COVID-19 compared with non-COVID-19 patients over time. Specifically, they compared COVID-19 patients with non-COVID-19 patients (including influenza and the 10 most common *International Classification of Diseases,* 10th Edition ICU diagnoses during and prior to the pandemic) and then performed a second analysis comparing the first wave of the COVID-19 pandemic (March–July 2020) with the second wave (October–December 2020).

The cohort included 479 COVID-19 ICU episodes and 19,744 non-COVID-19 ICU episodes. Patients with COVID-19 were younger and had

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more comorbidities but were less likely to be immunosuppressed or have cancer. The median ICU length of stay was significantly longer for COVID-19 patients (14 vs 2 d; $p < 0.001$) with a higher 30-day mortality (24% vs 15%; $p < 0.001$). Markedly, the longest median duration of ventilation in non-COVID-19 diagnoses was 5 days for ARDS but reached 10 days in COVID-19.

The proportion of VA-LRTI in ICU patients with COVID-19 was higher at 30% compared with 18% in patients without COVID-19. However, this difference was likely due to the longer duration of ventilation in COVID-19, a known risk factor for VAP (1). When adjusted for number of ventilator days at risk, the rate of VA-LRTI for patients with COVID-19 (31/1,000 ventilator-days) compared similarly to patients without COVID-19 (34/1,000 ventilator-days). Interestingly, this rate of VA-LRTI was higher in COVID-19 patients than that in other infectious causes of ICU stay (11/1,000 ventilator-days), namely, bacterial pneumonia, influenza, and severe sepsis.

Comparing the first wave of the pandemic with the second wave, the second wave included older patients with more comorbidities, steroid use, and prone positioning, although a shorter length of mechanical ventilation. The VA-LRTI proportion in the COVID-19 group increased from 29% (99/381) to 38% (30/93) from the first to the second wave with a minimal change of 19% (37/567) to 21% (28/324) in the non-COVID-19 group. After multivariable analyses, the second wave had a significantly higher adjusted cause-specific hazard ratio (1.86 [95% CI, 1.15–3.01]) and adjusted subdistribution hazard ratio (1.81 [95% CI, 1.17–2.79]) compared with the first wave.

How do we reconcile the various previous studies that have reported a significant increase in VAP rates in patients with COVID-19 (2–8, 10–14) with this finding of no increase from Hedberg et al (9)? The first explanation may be related to the very high rate of VA-LRTI in the control arm of Hedberg et al (9) study: 34 per 1,000 ventilation-days, compared with lower control arm rates from previous studies: 13 per 1,000 ventilation-days (3) and 15 per 1,000 ventilation-days (2), which indicates that Hedberg et al (9) reported more than double the control baseline rate of other studies; thus, if patients without COVID-19 were already at such a high risk for VAP (9), it might have become not feasible to detect any VAP rate difference compared with patients with COVID-19. A second explanation is that the infection definitions (e.g., VAP and VA-LRTI) used in these studies were different and not amenable to comparison. Another surveillance definition, ventilator-associated events (VAEs), has also been evaluated and shown higher VAEs per 100 episodes of ventilation, but similar VAEs rates per 1,000 ventilator-days in patients with COVID-19 versus those without COVID-19 (15). A third explanation is regarding the multiple limitations associated with all these studies done during the pandemic: no reporting and analysis accounting for standardized infection control measures, no collection of local baseline rates of VAP, no data on availability and turnover of hospital and ICU beds, adequacy of the number of healthcare providers needed for each hospital and ICU size, access to and training of personal protective equipment, and use of concomitant medications that may cause further immunosuppression (e.g. steroids), thus increasing the risk of VAP or antivirals that may limit further progression of the viral disease and reduce the length of hospital stay (e.g., remdesivir), thus decreasing the risk of VAP. All of the above variables, individually or combined, may have biased these studies either way, that is, increasing or decreasing the detection of any potential differences in the VAP rates between patients with and without COVID-19. A fourth explanation may stem from the use of absolute versus relative rates of VAP, both of which can produce discrepant interpretations even though reflecting the same actual frequency of infection; for example, although the absolute rate of VAP may be increased with COVID-19, the rate relative to baseline disease severity, age, comorbidities, and hospital length of stay may not show the same increase. Finally, the different methods for statistical adjustment (linear, logistic, Cox, Fine-Gray, and subdistribution regression models) may produce different VAP rates.

One thing we can say with certainty: patients hospitalized with COVID-19 are undoubtedly requiring longer hospital/ICU stay and prolonged mechanical ventilation duration, are more frequently proned, and are receiving more immunosuppressive drugs

than any other respiratory viral infection ever before. These three variables above have been well-known risk factors for VAP for a long time, even before the COVID-19 pandemic. Thus, it should come as no surprise that we are actually seeing an increased absolute rate of VAP during this pandemic; however, the question that remains is after adjusting for all relevant variables, whether the relative rate of VAP is increased. Until we have prospective cohort studies with more granular and systematic data collection regarding infection control measures, baseline hospital rates of VAP/VA-LRTI/VAE, hospital and ICU capacity, noninvasive and invasive respiratory support availability and utilization, baseline disease severity, concomitant use of antiviral and immunosuppressive drugs, and statistical methods for the appropriate adjustments, the "relative rate puzzle" remains unknown, but the "absolute rate puzzle" is already known.

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