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What COVID-19 Has Taught Us
Ventilator-associated Pneumonia Is Back!

Ventilator-associated pneumonia (VAP) has been a common source of ICU infection, morbidity, and mortality for many years, but recently, the use of "ventilator bundles" and other prevention efforts has led to the belief that "zero VAP" is an achievable goal, and that many episodes of VAP are the result of medical error (1). However, since coronavirus disease (COVID-19) became a reality in our ICUs, we have seen once again high reported rates of VAP (typically 40%), and in one study, VAP was associated with a higher 28-day mortality rate in patients with COVID-19 than in those with influenza or no viral infection (2, 3). In another study of 774 patients with COVID-19, 46% had hospital-acquired infections, of which VAP was the most common (4). These data make it clear that during COVID-19, "VAP is back", and many questions have emerged (5). Was VAP ever really gone, or is COVID-19 changing its epidemiology? In the COVID-19 pandemic era, does VAP occur as often in patients without COVID-19 as in those with COVID-19? And finally, what are the mortality implications of VAP in patients with COVID-19? Specifically, is VAP a terminal event, or does it independently add to the risk of death for both individual patients and the population as a whole?

Many of these issues are addressed in a study in this issue of the *Journal* by Vacheron and colleagues (pp. 161–169) using the REA-REZO French ICU Surveillance network, including over 70,000 patients: 64,816 control patients before COVID-19, 7,442 patients in the COVID-19 pandemic without COVID-19, and 1,687 patients with COVID-19 (5). Their goal was to study VAP in each population and

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define its incidence, mortality rate, attributable mortality (AM) percent, and attributable fraction of mortality. For the control group, pandemic patients who were COVID-19 (–), and patients who were COVID-19 (+), the incidence of VAP was 14.2, 18.3, and 31.9 episodes per 1,000 ventilator days, respectively. These data show that both pandemic groups had a significantly higher incidence of VAP than the control group, but the reasons that pandemic conditions raised the rate of VAP were unclear. Even the pandemic patients without COVID-19 had a hazard ratio of 1.28 for developing VAP compared with control patients. Maybe this is the result of it now being "politically acceptable" to recognize VAP, or maybe pandemic-related nurse–patient ratios and implementation of ventilator bundles have changed, and these factors led to more VAP. While pandemic conditions increased the incidence of VAP, the AM and attributable fraction of mortality at 60 and 90 days were higher only in the pandemic patients who were COVID-19 (+) and not the other populations. At 90 days, for patients who were COVID-19 (+), the AM was 8.1%, and the attributable fraction of mortality was 9.2%. Thus there is something unique about COVID-19 that leads to both a high rate of VAP and higher excess mortality, and this needs to be better understood. These findings could be the result of the disease itself or the therapies used in these patients, particularly corticosteroids and immune suppression (which are not reported in the current study, although COVID-19 patients had a higher rate of *Aspergillus* infection than other groups). Because the analysis was conducted using a large database, it was impossible to evaluate the impact of factors such as timely diagnosis, therapy, and accurate therapy, all known from prior studies to impact the AM of VAP.

To understand the importance of these data, it is necessary to review the history of VAP AM and the factors that add to it compared with the VAP AM fraction. AM refers to what percentage of deaths in individual patients occurred as the result of VAP, and not just because of underlying serious illness. Early studies of AM reported rates greater than 50%, while more recent studies reported rates between 5% and 10% (6–8). These large discrepancies reflect both methodology and the patient populations studied. Recent studies have looked at mortality and discharge from ICU as competing endpoints and used multistate modeling (MSM) to estimate AM, accounting for time-dependent confounding of the estimation of AM (8–10). In a Belgian study of 2,720 patients in the ICU treated with mechanical ventilation, 210 developed VAP (9), and multiple MSM approaches found AM to be no more than 5% at Day 60. The preferred MSM model accounted for the time-dependence of VAP and comorbid factors, finding an AM at 60 days of 3.6%. A meta-analysis of 24 studies reported an overall AM of 13%, with higher rates in surgical patients and those with intermediate disease severity (APACHE [Acute Physiologic Assessment and Chronic Health Evaluation] score of 20–29), and nearly no AM in trauma and medical patients with very low (likely to survive regardless of VAP) or very high (likely to die independent of VAP) APACHE scores (8). AM is also affected by the accuracy of supportive care, with mortality being directly impacted by the use of timely and appropriate therapy (10). The attributable fraction mortality of VAP is somewhat different from AM and, unlike AM, is dependent on the frequency of VAP and thus the efficacy of VAP prevention measures. If VAP were highly preventable, very few of the patients who died would have VAP as a cause, while among those with VAP, AM would depend on patient and therapy factors independent of the incidence of the illness.

The finding that, despite ventilator bundles, VAP in patients who were COVID-19 (+) had a higher AM and attributable fraction than VAP in the nonpandemic era, and then in VAP among patients who were COVID-19 (–) in the pandemic period, suggests that patients with COVID-19 may need a specific approach to VAP management and prevention. This approach still needs to be defined, but will likely require accurate diagnosis, timely and appropriate therapy (targeting the same pathogens as in traditional VAP), limitation of indiscriminate antibiotic use during the ICU stay, and minimizing the prolonged use of immunosuppressive therapy. In addition, unique prevention strategies may be needed, one of which could include the use of novel endotracheal tubes designed to prevent biofilm formation or the use of selective digestive decontamination (SDD), which is not a common practice in most ICUs. In one small study, SDD consisted of 5 days of systemic antibiotics together with topical oral and intestinal antibiotics, intranasal mupirocin, and daily chlorhexidine baths for the duration of mechanical ventilation. This intervention led to a reduction in VAP from 23.5 to 9.4 episodes per 1,000 ventilator days ($P < 0.001$) when compared with ICUs that did not use SDD (11).

Clearly, COVID-19 has reintroduced us to the challenges presented by VAP. Not only is it now clear that "VAP is back", but we must find ways to combat it among patients with COVID-19, well beyond the current approach of using VAP bundles alone, which have had limited value during the pandemic, especially among patients who were COVID-19 (+). ■

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There Will be Blood—But Maybe Less with Prostaglandin E_1

Although there may be disputes over its efficacy, there are few people left who do not think that venovenous extracorporeal membrane oxygenation (VV-ECMO) is lifesaving to some extent in patients with acute respiratory distress syndrome (ARDS); this belief has been reflected by a sharp increase in its deployment over the last decade despite lack of clear positive randomized controlled trials (1). The question remains to what extent and for which patients is ECMO lifesaving, as mortality is still close to 50% in observational studies (2). One of the problems is that the benefits in terms of lifesaving are offset by complications of ECMO support itself. Analogously to, for example, the case of patients with hematological malignancies, mortality is in part disease-related, but there is also significant treatment-related mortality.

Exposure of blood to the nonbiologic surfaces of an extracorporeal circuit initiates a complex inflammatory response involving both the coagulation and the inflammatory response pathway. Historically, the most feared complication is a thromboembolic stroke due to extracorporeal system-induced clotting activation, for which systemic anticoagulation, usually with unfractionated heparin with an aPTT (Activated Partial Thromboplastin Clotting Time) target of 2.0–2.5 times baseline, is necessary.

Or is it? Perhaps not, or at least that belief has been challenged by recent data on thromboembolic and hemorrhagic complications in cohort studies. For example, a cohort study in which 61 VV-ECMO patients were treated with a prophylactic dosage of LMWH (Low Molecular Weight Heparin) found fewer bleeding complications and no ischemic strokes, although in 5 patients the pump unexpectedly stopped due to thrombotic occlusion (3). Thus, omitting anticoagulation may be too revolutionary a step; however, severe thromboembolic complications like ischemic stroke seem to occur less often and are far outnumbered by severe hemorrhagic complications including hemorrhagic stroke, which were present up to 21% in autopsy studies in patients with coronavirus disease (COVID-19) who died in spite of being supported with VV-ECMO (4). This is in part explained by improved materials and the use of heparin-coated cannulas. More importantly, there seems to be no relationship between the level of anticoagulation and the occurrence of a rare thromboembolic stroke; however, there is a strong relationship between the level of anticoagulation and the frequent occurrence of bleeding complications (55%) as well as the need for a blood transfusion, both of which are directly related to poor outcome (5). Moreover, fatal hemorrhagic stroke is far more frequent than fatal thromboembolic stroke (6). Taken together, one might postulate that anticoagulation with heparin during ECMO might lead to more problems than benefits. However, there is a paucity of studies evaluating different anticoagulation strategies in patients supported with ECMO and no randomized trials comparing one strategy with another. A comprehensive guideline from Extracorporeal Life Support Organization for the use and monitoring of anticoagulation during ECMO support has been recently published, but this guideline stops short of any mandate, given the lack of evidence in favor of most of the practices reviewed (7). Rigorous evaluations of anticoagulation use in ECMO patients are, therefore, urgently needed (8).

Therefore, we welcome the performance of pharmacological studies in which the primary aim is the optimization of anticoagulation during ECMO support. In this issue of the *Journal* (pp. 170–177), Buchtele and colleagues share the results of a phase-II RCT in which 5 ng/kg/min prostaglandin E_1 (PGE_1) in addition to low dose heparin was compared with heparin alone in patients supported by VV-ECMO (9). Both groups included 24 patients. The hypothesis, based on experiences with renal replacement therapy, was that the addition of PGE_1 could extend the lifespan of the ECMO circuit, but as this was a safety study, the primary outcome was the rate of transfused packed red cells per day of ECMO support. The transfusion rate was similar between groups (0.41 versus 0.39; $P = 0.733$). Fewer patients in the PGE_1 group had any membrane lung clotting (7 versus 16; $P = 0.020$) and the time to first membrane change was longer in patients allocated to PGE_1 (hazard ratio 0.30; 95% confidence interval 0.12–0.75). These findings suggest that the addition of PGE_1 to heparin might extend the lifespan of the ECMO circuit, although it is not clear by how long exactly, without an increase in hemorrhagic complications as reflected by similar blood transfusions in both groups. The secondary endpoints even suggest a reduction in thromboembolic *and* bleeding events with PGE_1 administration, but given the pharmacological features of PGE_1, inhibition of platelet aggregation and arterial vasodilatation, the mechanism by which that would work is obscure. As blood pressure

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