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Commentary

Caution, not causality: The limitations of risk factor and outcome research on ventilator-associated events

Kelly A. Cawcutt MD, MS and Trevor C. Van Schooneveld MD
Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, Nebraska

Ventilator-associated events (VAEs) have been used by the National Healthcare Safety Network (NHSN) since 2013, when the more subjective ventilator-associated pneumonia (VAP) definition was retired. Since that time, continued debate on the utility of VAE as a definition has existed. The VAE definition is significantly more objective due to relying upon distinct measures of oxygenation (fraction of inspired oxygen [Fi02] and positive end-expiratory pressure [PEEP]), as opposed to previously utilized clinical definitions but now encompasses a much broader group of disorders beyond pneumonia, including pulmonary edema, atelectasis, mucus plugging, abdominal disorders and sepsis, which may impact lung function, pulmonary embolism, and transfusion-related lung injury.[1,2] Discordance between clinical VAP and VAE has been well described in which VAE surveillance has not correlated with traditionally defined VAP cases.[2,3] Additionally, recommended prevention strategies for VAP may not necessarily impact VAE, and compliance with VAP bundles has not correlated with improvement in VAE rates.[4] These reports have raised questions regarding the value of VAE as a metric for patient care or outcomes.

Previous studies have described the impact of VAE as a clinical outcome, noting worse prognosis for patients with VAEs compared to those without.[1,2] Controversy regarding these results remains due to concerns over sample size, study design, and ability to control for confounders. Additional research is required to determine the impact of VAE on meaningful patient centered outcomes, to better define the risk factors for VAE, and then to identify practical and effective preventative measures. To gain further understanding, Zhu et al[5] studied >30,000 intensive care unit (ICU) patients seeking to define the impact of VAEs on ICU length of stay (LOS), hospital LOS, hospitalization costs, days of mechanical ventilation, failure to extubate prior to ICU discharge, mechanical ventilation for ≥9 days, and mortality (death in the ICU from all causes, and predicted death on ICU discharge).

This study was performed at a large institution in China using CDC VAE definitions to electronically identify VAE events. Over nearly 4 years, 30,830 patients were admitted to the ICU with 6,426 meeting the inclusion criteria of mechanical ventilation for ≥4 days. The study matched VAE cases to non-VAE controls 1:2 match using the mentioned inclusion criteria. Interestingly, 28% of all patients spending at least 4 days on a ventilator developed a VAE (1899 events) with 1,172 VACs, 536 infection-related ventilator-associated complications (IVACs), and 191 PVAPs. Major baseline differences were detected between the VAE and non-VAE groups, specifically in APACHE II, chronic lower respiratory tract infection surgical intervention, and many of the outcomes of interest. The authors evaluated 7 of the 8 outcomes of interest using propensity scoring matching with numerous variables in an attempt to account for these differences. They were unable to analyze duration on a ventilator because the populations could not be well matched. In all other analyses, outcomes were significantly worse in the group with VAE, and this persisted when the authors performed multivariate regression and sensitivity analyses. VAE subtype (VAC, IVAC, or PVAP) analysis demonstrated no difference in LOS, but IVAC and PVAP had increased duration of mechanical ventilation. Risk factors identified for mortality included older age, high APACHE II scores on ICU admission, presence of pneumonia, need for blood transfusion, immunosuppressive medications, presence of central venous catheters, and ≥2 VAE episodes during an ICU stay. Surgical operations and tracheotomy were associated with lower risks of mortality.

The clear strengths of this study include the large cohort of patients, standardized surveillance using established CDC methodology, and robust analyses of multiple outcomes. These findings strongly support that VAE development portends multiple worsened outcomes. These findings also support the argument that VAE identification is clinically meaningful and that it may be a useful quality metric. Quality metrics that detect conditions that impact patient outcomes are ideal, but they are most useful when they can be coupled with well-established mitigation strategies. Unfortunately, high-quality evidence regarding optimal prevention strategies for VAE are lacking, and previously used strategies for VAP prevention have not proven useful in VAE prevention.[2,4] Evidence-based recommendations exist for prevention of VAP, but many are based on moderate or low-quality evidence, resulting in debate regarding overall utility.[1] These interventions can also easily fail if they are ineffectively implemented. VAE prevention is a difficult task because the condition represents a mixture of conditions ranging from pneumonia to volume overload to pulmonary embolism and more; therefore, prevention strategies must be multifaceted. The most effective interventions for VAE prevention and subsequent VAP prevention may be strategies that decrease duration of mechanical ventilation and therefore time at risk for VAE. Trials utilizing spontaneous awakening and breathing trials have demonstrated decreased time on the ventilator and decreased VAE rates.[2,6–8] These

Author for correspondence: Kelly Cawcutt, E-mail: kelly.cawcutt@unmc.edu
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strategies, coupled with minimization of sedation, early mobility, use of low tidal ventilation, and conservative fluid and blood product, have all shown some success in decreasing the conditions associated with VAE (eg, pneumonia, atelectasis, acute respiratory distress syndrome (ARDS), pulmonary edema, and more).[1,7,8]

We suggest focusing on PVAPs rather than the entire VAE umbrella. This is a cautionary statistical tale of weighting association as causality. First, VAE, with VAC, is the gatekeeper to reach PVAP, comprising the minority of patients within the group (only 10% of the VAEs met PVAP criteria). If outcomes are worse for all VAEs, the argument to prevent PVAP alone is weakened, and preventing VAEs prevents PVAPs. We also appropriately suggest caution regarding the risk of blood transfusions and central venous catheter placement in the ICU for VAE. This study does not have the strength in design or results to determine whether transfusion or CVCs have a causal role, nor can the results be extrapolated to state avoidance of transfusion or CVC placement could prevent VAEs. Because severity of illness was only assessed on ICU admission, these may simply be markers of level of illness. Additionally, blood transfusions have been associated with negative immune modulation, and numerous studies have found more aggressive transfusion strategies to be associated with negative outcomes, further confounding the situation.[9]

Worse patient outcomes are increasingly attributed to VAEs, suggesting that surveillance and metric reporting carry value. However, optimal preventative strategies remain unclear. The focus is no longer simply on preventing pneumonia but requires a multifaceted, holistic approach to hasten liberation from mechanical ventilation. Further prospective studies on specific strategies to mitigate the impact of VAE on patient-centered outcomes are needed.

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