Ventilator-Associated Events: What They Are and What They Are Not

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In 2013, the United States Centers for Disease Control and Prevention redefined surveillance for quality of care in ventilated patients by shifting from ventilator-associated pneumonia (VAP) definitions to ventilator-associated event (VAE) definitions. VAE definitions were designed to overcome many of the limitations of VAP definitions, including their complexity, subjectivity, limited correlation with outcomes, and incomplete capture of many important and morbid complications of mechanical ventilation. VAE definitions broadened the focus of surveillance from pneumonia alone to the syndrome of nosocomial complications in ventilated patients, as marked by sustained increases in ventilator settings after a period of stable or decreasing ventilator settings. Qualitative studies suggest that most VAEs are caused by pneumonia, fluid overload, ARDS, and atelectasis. Only about 40% of clinically diagnosed VAPs meet VAE criteria, likely because the VAE requirement for a sustained increase in ventilator settings sets a threshold effect that selects for patients with severe disease. VAEs are associated with a doubling of the risk of death compared to patients without VAEs and compared to patients who meet traditional VAP criteria. Risk factors for VAEs include sedation with benzodiazepines or propofol, volume overload, high tidal-volume ventilation, high inspiratory driving pressures, oral care with chlorhexidine, blood transfusions, stress ulcer prophylaxis, and patient transport. Potential strategies to prevent VAEs include minimizing sedation, paired daily spontaneous awakening and breathing trials, early mobility, conservative fluid management, conservative transfusion thresholds, and low tidal-volume ventilation. A limited number of studies that have tested subsets of these interventions have reported substantial decreases in VAEs; no group, however, has thus far assessed the impact of a fully optimized VAE prevention bundle that includes all of these interventions upon VAE rates and other outcomes. *Key words: ventilator-associated events; ventilator-associated pneumonia; quality improvement; surveillance; infection prevention and control.* [Respir Care 2019;64(8):953–961.

Introduction

Ventilator-associated event (VAE) definitions were first released by the United States Centers for Disease Control and Prevention (CDC) in 2013. The CDC created VAE definitions to replace their longstanding surveillance definitions for ventilator-associated pneumonia (VAP). The VAE concept was designed to overcome many of the limitations of traditional VAP definitions including their subjectivity, complexity, and limited association with mortality. VAE definitions by contrast were designed to be objective, reproducible, automatable, and strong predictors of poor outcomes. This article reviews the limitations of traditional VAP surveillance, the CDC's rationale for creating VAE definitions, comparative literature on VAE versus VAP surveillance, risk factors for VAEs, and best practices to prevent VAEs.

Limitations of Traditional VAP Surveillance

For many years, VAP was the de facto measure of quality of care for ventilated patients. Hospital infection-prevention programs invested heavily in preventing VAP by implementing ventilator bundles and tracking VAP rates. Over time, however, many concerns were raised about the validity, reproducibility, and interpretation of VAP rates, particularly in the context of public reporting and benchmarking.[1,2] Surveyors and quality managers noted that VAP surveillance is highly subjective. The traditional surveillance definition for VAP included criteria such as "a new or progressive infiltrate," "worsening oxygenation," and a "change in the quality or quantity of sputum."[3] While these criteria mirror traditional bedside diagnostic criteria for VAP, they are very subjective and thus allow different surveyors to come to different conclusions about whether a given patient meets CDC criteria for VAP. In 1 study, for example, 3 different surveyors independently applied CDC VAP criteria to 50 different patients with respiratory deterioration.[4] Individually, the 3 reviewers identified 11, 15, and 20 VAPs, respectively; collectively, all 3 reviewers agreed on just 7 VAPs. In another study, investigators distributed 6 case vignettes to 43 infection control experts across the United States and asked them to comment on how many of the 6 cases met CDC criteria for VAP.[5] Almost equal numbers of respondents thought that 1, 2, 3, 4, or 5 of the 6 patients met VAP criteria. High levels of inter-observer variability undermine the meaningfulness and appropriateness of using VAP rates to compare hospitals because it is impossible to know if observed differences are due to variations in quality of care or differences in surveillance determinations.[1]

Investigators have noted other problems with using VAP rates to measure quality of care for ventilated patients. Hospitals' favored diagnostic procedures, for example, can have a large impact on perceived VAP rates. One hospital documented a 4-fold variation in VAP rates depending on whether they permitted positive endotracheal aspirate cultures with any amount of growth to confirm VAP status versus requiring positive bronchoalveolar lavage cultures with $\geq 10^4$ colony-forming units per milliliter.[6] In practice, however, neither qualitative endotracheal aspirate cultures nor quantitative bronchoalveolar lavage cultures are perfectly accurate indicators of VAP relative to histology (sensitivities are 75% for endotracheal aspirate vs 57% for quantitative bronchoalveolar lavage culture; positive predictive values are 61% vs 77%, respectively).[7] Another issue noted by many hospitals is the high degree of discrepancy between surveillance determinations of VAP versus clinical determinations of VAP.[8-11] One hospital, for example, observed a 7-fold variation in their VAP count using clinical criteria versus CDC surveillance criteria.[9]

Implications for Prevention

A more insidious problem with traditional VAP definitions is that they can lead to potentially spurious impressions about the effectiveness of different VAP prevention strategies. The issue is that the subjective and nonspecific nature of VAP criteria allow for two kinds of errors: their subjectivity makes it possible that lower VAP rates after implementing a new initiative are due to stricter application of subjective surveillance criteria rather than a true decrease in bona fide pneumonias, and their lack of specificity allows for circularity between prevention measures' mechanisms of action and VAP criteria.[12] For example, oral care with chlorhexidine may decrease the frequency of positive cultures from the oropharynx, which in turn will lead to fewer perceived VAP cases, but positive cultures are neither perfectly sensitive nor perfectly specific indicators of VAP.[7] Similarly, endotracheal tubes with sub-

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glottic secretion drainage may decrease the volume of pulmonary secretions, which in turn could lead to fewer perceived VAP cases, but the volume and character of pulmonary secretions are neither sensitive nor specific for VAP.[13]

These 2 potential sources of error apply as much to ventilator bundle initiatives as they do to studies of targeted prevention strategies. Numerous institutions have reported dramatic decreases in VAP rates after implementing ventilator bundles. Similarly, there has been a parallel decrease in the incidence of VAP reported to the National Healthcare Safety Network; the median VAP rate for nonteaching medical and medical-surgical units immediately prior to the introduction of VAE definitions was zero.[14] Interpreting the drop in VAP rates, however, is challenging.[15] By nature, bundle implementations are done in an open-label fashion. Surveyors involved in quality-improvement programs have a natural interest in being able to report success. This may lead to an unintentional bias toward applying subjective surveillance criteria more strictly. More insidiously, well-intentioned efforts to make surveillance more rigorous (eg, by requiring consensus between multiple surveyors, requiring quantitative bronchoalveolar lavage cultures to confirm VAP, or being very strict when applying surveillance criteria) will inevitably lead to lower VAP rates, even though these changes in and of themselves are independent of patient care.[16] A telling independent audit of VAP rates conducted by the Centers for Medicare and Medicaid Services found that VAP rates in United States hospitals were essentially stable between 2005 and 2013, in stark contrast to the dramatic decrease in VAP rates reported by hospitals to CDC.[17]

The Genesis of VAE Definitions

Recognizing the many limitations of VAP rates to measure quality of care or to benchmark hospitals, the CDC began convening representatives from a broad array of professional societies in 2011 to devise an alternative strategy for measuring safety and quality in ventilated patients.[18] This working group suggested shifting the focus of surveillance from pneumonia in particular to the syndrome of nosocomial respiratory deterioration in general.[19] This shift offered 2 major advantages over traditional VAP surveillance. It broadened the focus of prevention from pneumonia alone to encompass all major causes of respiratory deterioration in ventilated patients (ie, pneumonia *plus* pulmonary edema, ARDS, pulmonary embolism, atelectasis, etc.). The shift also allowed for the possibility of substantially simplifying and even automating surveillance because the surveillance definition only needed to identify objective markers of respiratory deterioration—it did not need to identify pneumonia in particular. These two ideas became the basis for VAE definitions.

The CDC defined a VAE as a sustained increase in ventilator support following a period of stable or decreasing ventilator support.[18] The definition is operationalized using 2 ventilator settings, PEEP and F_{IO_2}. In practice, a VAE is defined as either 2 or more baseline days of stable or decreasing daily minimum PEEP values followed by at least 2 days of daily minimum PEEP values $\geq$ 3 cm H_2O above each of the 2 baseline days' values, or 2 or more baseline days of stable or decreasing daily minimum F_{IO_2} values followed by at least 2 days of daily minimum F_{IO_2} values $\geq$ 20 points above each of the 2 baseline days' values.

The VAE definition also includes subcategories to try to identify the subset of VAEs that might be due to infection and the subset of infection-related VAEs that may be due to pneumonia. The infection-related subset is called infection-related ventilator associated complications (IVAC) and is defined as the presence of an abnormal temperature ($<$ 36°C or $>$ 38°C) or white blood cell count ($\leq$ 4,000 cells/mm^3 or $\geq$ 12,000 cells/mm^3) as well as $\geq$ 4 days of new antibiotics starting within 2 days of VAE onset. Possible VAP in turn is defined on either histological grounds or as the subset of IVACs with concurrent positive respiratory cultures or positive microbiological assays for *Legionella* species or respiratory viruses. The culture criterion can be fulfilled in either of 2 ways: growth above a specified quantitative threshold tailored to the specimen type (eg, endotracheal aspirate with $\geq 10^5$ colony-forming units/mL vs bronchoalveolar lavage with $\geq 10^4$ colony-forming units/mL vs protected specimen brush sample with $\geq 10^3$ colony-forming units/mL) or any amount of growth paired with Gram stain findings of purulence ($\geq$ 25 neutrophils and $\leq$ 10 epithelial cells per low-powered field). It should be noted that while the VAE criteria for possible VAP are more objective than traditional VAP criteria, there are no data to suggest they are any more (or less) accurate than traditional criteria.

The Epidemiology of VAEs

Nearly 2,000 U.S. hospitals reported their VAE rates to CDC in 2016.[20] The overall VAE rate for critical care units nationwide was 6.8 events per 1,000 ventilator-days, but rates varied substantially by ICU type. VAE rates tend to be higher in trauma, surgery, and neuroscience units and lower in medical and cardiac units.[21] Similarly, VAE rates tend to be higher in major teaching hospitals and lower in non-major teaching hospitals.[21] Risk for developing VAEs tends to be highest in the first 2 weeks of mechanical ventilation (particularly days 3–7), but patients remain at risk until extubation.[22] Approximately one third of VAEs fulfill IVAC criteria, but this varies widely by unit type: almost half of all VAEs in trauma, burn, and surgery units nationwide met IVAC criteria in the CDC's most recent

Table 1. VAEs: What They Are and What They Are Not

	VAEs	
	What They Are	**What They Are Not**
Intent	**VAE is a surveillance concept:** Designed to be applied retrospectively to populations of patients to identify broad opportunities for quality improvement and to assess the impact of quality improvement initiatives.	**VAE is not a clinical diagnosis:** The VAE concept was not designed to support real-time clinical diagnoses or to inform real-time clinical care for individuals.
Surveillance	**VAE surveillance is objective and reproducible:** Based on changes in ventilator settings; amenable to automated surveillance by computers; no room for differences of opinion between different surveyors or between clinicians and surveyors.	**VAE is neither sensitive nor specific for VAP:** VAE's sensitivity and specificity for clinically diagnosed pneumonia is low; VAE surveillance only identifies severe pneumonias that require increased ventilator support; VAEs can be caused by many conditions other than pneumonia.
Etiology	**VAEs have many potential causes:** Most common are pneumonia, fluid overload, atelectasis, and ARDS.	**VAEs are not a proxy for pneumonia.**
Morbidity	**VAEs are highly morbid:** VAEs are associated with increased length of stay and increased risk of death.	**VAEs are not benign.**
Prevention Strategy	**VAE surveillance provides an opportunity for hospitals to rethink their ventilator bundles:** Select interventions that reduce the duration of mechanical ventilation and that target the common causes of VAEs; examples include minimizing sedation, paired daily spontaneous awakening and breathing trials, low tidal-volume ventilation, early mobility, conservative fluid management, and conservative transfusion thresholds.	**VAEs are not fully preventable using traditional ventilator bundles.** 1. Some aspects of traditional ventilator bundles may be harmful (eg oral care with chlorhexidine and stress ulcer prophylaxis). 2. Traditional bundles are missing some potentially helpful interventions (eg, conservative fluid management, early mobility, and low tidal-volume ventilation).

VAE = ventilator-associated event
VAP = ventilator-associated pneumonia

surveillance report versus only one third of VAEs in medical units.[21] Within unit types, however, VAE rates and the fraction that qualify as IVACs also vary widely. The overall hospital mortality rate for VAEs reported to CDC in 2014 was 31%.[21] Patients who develop VAEs are about twice as likely to die compared to similar patients who do not develop VAEs.[23-26]

Concordance Between VAE and Traditionally Defined VAP

A number of studies have evaluated the overlap between VAE and traditionally defined VAP. Fan and colleagues[27] summarized these studies in a meta-analysis that included data from 18 studies conducted in 8 countries that collectively enrolled 61,489 subjects. The pooled sensitivity of VAE for traditionally defined VAP across 11 studies and 1,633 subjects was 42% (95% CI 18–66%). The pooled positive predictive value of VAE for traditionally defined VAP across 9 studies and 3,572 subjects was 23% (95% CI 13–34%). Subjects with VAEs were more likely to die compared to subjects with traditionally defined VAPs (pooled odds ratio for death in subjects with VAE vs VAP 1.49, 95% CI 1.11–2.01, and with IVAC vs VAP 1.76, 95% CI 1.23–2.52).[27]

Discordance Between VAE and Traditionally Defined VAP

The mismatch between VAE and traditionally defined VAP has been a source of concern for people considering VAE surveillance. The key consideration when interpreting the discordance is to recall that VAE was intentionally designed to be different from VAP (Table 1). VAE is not a proxy for VAP, rather it is a new and unique entity unto itself. One of the explicit goals of VAE surveillance was to broaden the scope of safety surveillance for ventilated patients to encompass a broad range of potential nosocomial complications, not just pneumonia alone. This explains the low positive predictive value of VAE surveillance for VAP: it is both expected and desirable that many VAEs will be conditions other than pneumonia. The high absolute mor-

tality rate associated with VAE and the increased odds of death for patients with VAEs versus those with traditionally defined VAP affirm the clinical importance of the extra events detected by VAE surveillance.

VAEs' low sensitivity for traditionally defined VAP at first blush is more concerning. The fact that VAE surveillance "misses" many traditionally defined VAPs would appear to undermine its claim to detect clinically important respiratory complications of care. In practice, however, VAE surveillance is imposing a severity threshold and only counting the most severe pneumonias, namely those that are associated with clear evidence of respiratory deterioration. This explains why the relative mortality rate for VAE is higher than traditionally defined VAP.[27] By definition, a VAP that does not meet VAE criteria is one in which there is no significant increase in ventilator support following a period of stability or improvement. This is an important aspect of VAE surveillance given the very high rate of overdiagnosis of pneumonia. Both clinical audits and autopsy series report that 40–70% of clinical diagnoses of VAP are incorrect.[28-31] Deterioration in gas exchange is considered one of the diagnostic hallmarks of pneumonia and a potent predictor of worse outcomes.[32-34]

The absence of impaired gas exchange by contrast is associated with a more benign clinical course.[24] Despite the conceptual and epidemiologic importance of impaired gas exchange in establishing a diagnosis of pneumonia, clinical series suggest that up to 50% of patients diagnosed with VAP have stable ventilator settings, thus accounting for the low sensitivity of VAE.[35,36] These patients appear qualitatively different from patients with impaired gas exchange. One analysis, for example, found that subjects with clinically suspected pneumonia but minimal and stable ventilator settings did equally well if they were treated with very short courses of antibiotics (median 2 d) versus more conventional courses (median 8 d).[35] This is not to imply that pneumonias detected with VAE surveillance are necessarily more specific than traditionally defined VAPs relative to a reference standard such as autopsy—there are no studies that specifically address this question—but this does emphasize that VAE surveillance hones in on a subset of patients with more severe disease.

Surveillance Versus Clinical Care

The decision to focus VAE on the subset of patients with more severe disease belies the fact that VAE is a surveillance concept, not a clinical concept. This is evident insofar as VAEs are only apparent in retrospect (one has to wait 2 days after a patient first begins to deteriorate to see if a new increase in ventilator settings is sustained before one can know whether the patient had a VAE; this is obviously not useful for informing real-time clinical management decisions). The goals, and hence the methods, of surveillance are different from clinical care.[37] The emphasis in clinical care is on early diagnosis and rapid treatment, hence clinical definitions tend to favor sensitivity and speed over specificity. The emphasis in surveillance, by contrast, is on objectivity, reproducibility, and the detection of events associated with the most morbidity that need to be prioritized for prevention. Timeliness is less critical in surveillance because the results are not needed for immediate clinical decision-making on individual patients; rather the results are used to inform the selection and track the impact of prevention strategies at the population level. VAE definitions embody the ethos of surveillance rather than clinical care: they are based on objective clinical signs rather than subjective criteria, they are retrospective rather than prospective, and they focus on the subset of patients with severe disease.

Clinical Events Associated With VAEs

Multiple investigators have published case series of VAEs that included chart reviews designed to identify the clinical event that triggered an increase in ventilator settings and hence the VAE. The findings of these studies are relatively consistent. Most VAEs are triggered by 1 of 4 clinical events: pneumonia (25–40% of cases), fluid overload including pulmonary edema (15–50%), atelectasis (10–15%), and ARDS (5–20%).[38] A smattering of additional events are attributable to mucous plugging, pulmonary embolism, pneumothorax, poor pulmonary toilet, stroke, extrapulmonary sepsis syndromes, and transfusion-associated lung injury (Fig. 1). In about 10–20% of cases, there is no apparent reason for the escalation of ventilator settings. Knowing the events that typically trigger VAEs helps inform the selection of strategies to prevent VAEs.

Prevention of VAEs

The many differences between VAE and VAP compel a distinctive approach to prevention. One cannot simply apply the standard ventilator bundle (eg, head-of-bed elevation, oral care with chlorhexidine, spontaneous awakening and breathing trials, thromboprophylaxis, and stress ulcer prophylaxis) and expect that it will effectively prevent all VAEs. This is partly because VAP only accounts for a minority of VAEs and partly because the traditional ventilator bundle has been cast into doubt in recent years. New data question the appropriateness of some components (eg, oral care with chlorhexidine and stress ulcer prophylaxis) and suggest that there may be benefit in adding some new components (eg, conservative fluid management, conservative blood transfusion thresholds, early mobilization, and low tidal-volume ventilation). The introduction of VAE definitions provides an invitation to the critical care community to rethink ventilator bundles.

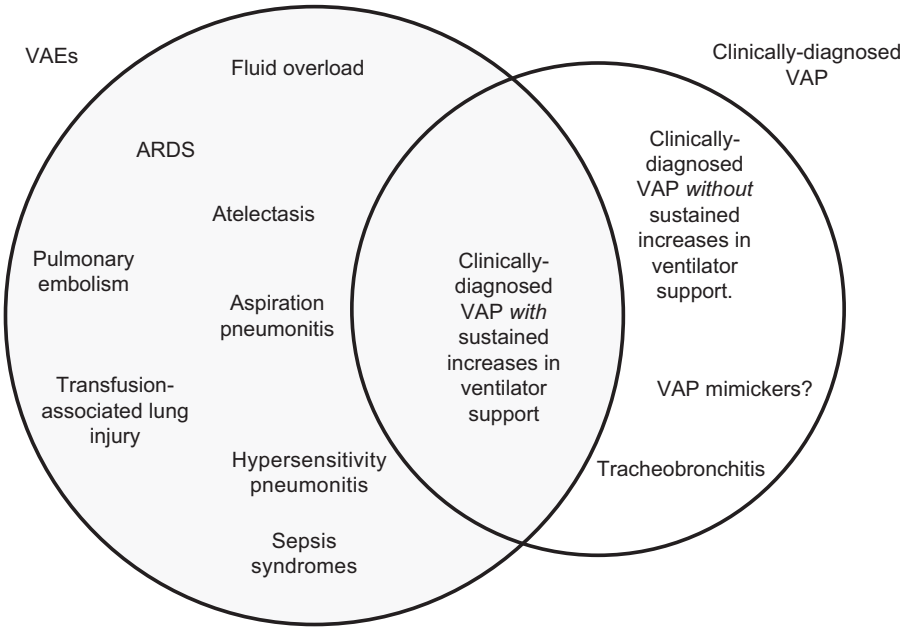

Fig. 1. Etiologies of ventilator-associated events (VAEs) and concordance with clinically diagnosed ventilator-associated pneumonia (VAP).

A few studies have evaluated the impact of traditional ventilator bundles on VAE rates and found that they have little impact.[39-41] There are a number of potential explanations for this. First, as noted, traditional VAP definitions are subjective, nonspecific, and prone to bias. This makes it difficult to interpret both randomized trials of individual prevention measures and implementation studies of VAP prevention bundles. In the case of the former, it is unclear whether lower VAP rates in the intervention arm reflect circularity between the prevention strategy and the VAP definition versus true decreases in VAP rates.[12] In the case of the latter, it is unclear whether observed decreases in VAP rates reflect better care or stricter application of VAP's subjective surveillance criteria.[15] Second, some components of traditional ventilator bundles may be harmful. Oral care with chlorhexidine, for example, may increase risk for VAEs and has been associated with higher mortality rates in some studies.[39,40,42-44] Likewise, stress ulcer prophylaxis may increase risk for hospital-acquired pneumonia including possible VAP as defined using VAE criteria.[40,45,46] VAE surveillance may be less vulnerable to misattributing benefit to neutral or negative interventions because VAEs are defined using objective ventilator data rather than subjective and nonspecific clinical signs. In addition, because VAE surveillance focuses on severe events, an intervention that reduces colonization alone is unlikely to show an impact on VAE rates.

The ideal VAE bundle is likely one that minimizes the time patients spend on mechanical ventilation and targets the conditions that most frequently trigger VAEs (eg, pneumonia, volume overload, ARDS, and atelectasis). Prevention is further informed by an analysis of potentially modifiable risk factors for VAEs. These include sedatives (especially benzodiazepines and propofol),[47-49] opioids,[47] positive fluid balance,[47,49-54] mandatory modes of mechanical ventilation with high tidal volumes and/or high inspiratory driving pressures,[47,50,53,55] blood transfusions,[51,52] oral care with chlorhexidine,[39] stress ulcer prophylaxis,[40] patient transport,[56] gastric retention,[49] re-intubation,[51] and neuromuscular blockade.[47,52,53] Conversely, dexmedetomidine, spontaneous awakening and breathing trials, and conservative fluid management appear to be protective against VAEs.[26,40,48,57,58]

Potential components of a ventilator bundle optimized to prevent VAEs could therefore include minimizing sedation, performing daily coordinated spontaneous awakening and breathing trials, mobilizing patients early, using conservative fluid management, setting conservative transfusion thresholds, and favoring low tidal-volume ventilation.[38] Elevating the head of the bed is also reasonable despite the paucity of data on this intervention insofar as the supine position is associated with increased risk of aspiration in patients receiving enteral nutrition; some limited data suggest that head-of-bed elevation may decrease VAP rates and perhaps time-to-extubation, and the intervention is cost-free and well embedded into current practice.[40,59-62] Notably, there does not appear to be any benefit to subglottic secretion drainage or tapered endotracheal tube cuffs. Randomized trials have failed to detect any salutary impact of either of these interventions on the frequency of VAEs, time-to-extubation, or mortality.[63-67]

Several intervention studies affirm that some of these potential bundle components are effective at lowering VAE rates. The Canadian Critical Care Trials Group organized a care improvement collaborative to help 11 ICUs implement the 2008 Canadian VAP prevention guidelines.[68] These guidelines only included a handful of the interventions proposed above, yet the group nonetheless observed a 29% decrease in VAE rates over a 20-month period.[26] In another study, investigators affiliated with the CDC Prevention Epicenters Program organized a care-improvement collaborative in 12 ICUs to prevent VAEs by increasing the frequency and reliability of paired daily spontaneous awakening and breathing trials.[57] Over a 19-month period, the monthly odds of VAEs dropped by 37%. A third care-improvement collaborative including 56 ICUs in Maryland and Pennsylvania worked together to implement a ventilator bundle (also not specifically optimized to prevent VAEs) and to improve unit-based safety culture, and over a 24-month period they also observed a 37% decrease in VAEs.[69] Finally, Mekontso Dessap and colleagues, in a randomized trial of depletive fluid management versus usual care in subjects being weaned from mechanical ventilation, reported that depletive fluid management was associated with a 50% decrease in the incidence of VAEs.[58]

Notably, none of these initiatives included all the components of the optimized ventilator bundle suggested above to prevent VAEs. Indeed, some of these care-improvement programs included some measures that might actually foster VAEs, such as oral care with chlorhexidine. These initiatives thus provide reassurance that VAEs can be prevented through better care but leave unanswered just how many VAEs could potentially be prevented by adopting a fully optimized bundle. Importantly, the more rigorous VAE and VAP prevention studies have not only reported lower VAE rates but also less time to extubation and hospital discharge.[57,58,70] A fully optimized VAE prevention bundle thus has the potential to not only substantially lower VAE rates but to also realize significant improvements in more patient-centered outcomes.

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