ORIGINAL ARTICLE

"Bundle" Practices and Ventilator-Associated Events: Not Enough

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OBJECTIVE. Ventilator-associated events (VAEs) are nosocomial events correlated with length of stay, costs, and mortality. Current ventilator bundle practices target the older definition of ventilator-associated pneumonia and have not been systematically evaluated for their impact on VAEs.

DESIGN. Retrospective cohort study.

SETTING. Tertiary medical center between January 2012 and August 2014.

PARTICIPANTS. All adult patients ventilated for at least 24 hours at our institution.

INTERVENTIONS. We conducted univariate analyses for compliance with each element; we focused on VAEs occurring within a 2-day window of failure to meet any ventilator bundle element. We used Cox proportional hazard models to assess the effect of stress ulcer prophylaxis, deep vein thrombosis (DVT) prophylaxis, oral care, and sedation breaks on VAEs. We adjusted models for gender, age, and Acute Physiology and Chronic Health Evaluation (APACHE) III scores.

RESULTS. Our cohort comprised 2,660 patients with 16,858 ventilator days and 77 VAEs. Adjusting for APACHE score and gender, only oral care was associated with a reduction in the risk of VAE (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.26–0.77). The DVT prophylaxis and sedation breaks did not show any significant impact on VAEs. Stress ulcer prophylaxis trended toward an increased risk of VAE (HR, 1.59; 95% CI, 1.00–2.56).

CONCLUSION. Although limited by a low baseline rate of VAEs, existing ventilator bundle practices do not appear to target VAEs well. Oral care is clearly important, but the impact of DVT prophylaxis, sedation breaks, and especially stress ulcer prophylaxis are questionable at best.

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Mechanically ventilated patients comprise a uniquely vulnerable population, and these patients frequently experience both morbidity and mortality. Best practice "bundles" have been proposed to manage this excess risk associated with ventilators, particularly ventilator-associated pneumonia (VAP).[1] The mechanically ventilated bundle includes measures to ensure that deep vein thrombosis (DVT) prophylaxis and stress ulcer prophylaxis are initiated, that oral hygiene is accomplished with chlorhexidine, that daily sedation breaks are taken, and that head-of-bed elevation is provided. This list addresses several preventable causes of healthcare-associated injury. Compliance with VAE bundles is effective in reducing VAP.[2,3] VAP is associated with prolonged hospitalization, intensive care unit (ICU) stay, ventilator requirements, and, possibly, increased mortality.[4–6]

However, detection of VAP is challenging. Initial symptoms are nonspecific, and there is no clinical gold standard for making the diagnosis. Existing definitions are complex and prone to low inter-rater reliability and reproducibility. In 2011, the Centers for Disease Control/National Healthcare Safety Network (CDC/NHSN) proposed a new definition for surveillance purposes, termed ventilator-associated events (VAEs).[7] In the VAE schema, a patient who experiences decompensation of any sort, infectious or otherwise while on the ventilator, has had a "ventilator-associated complication" (VAC). With clinical suspicion of infection, evidenced by fever, antibiotic use or white count, the event is an "infectious VAC" (IVAC). With further clinical and microbiological evidence, it can progress to the categories of "possible" and

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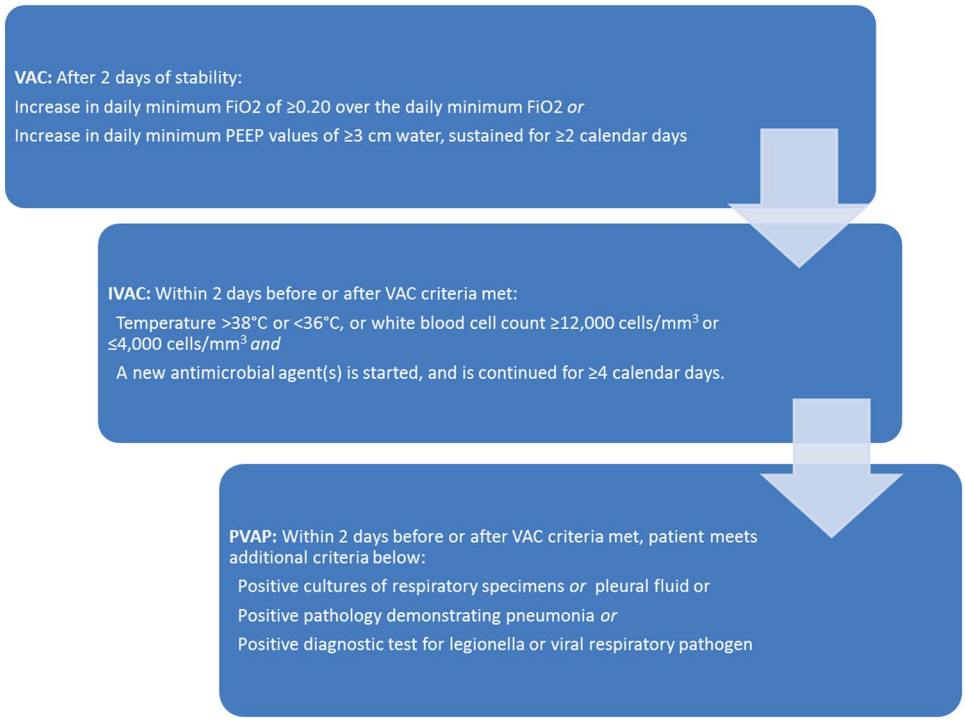

FIGURE 1. Simplified VAE criteria. Abbreviations: C, Celsius; cm, centimeters; FiO_2, fraction of inspired oxygen; IVAC, infectious ventilator-associated complication; mm, millimeters; PEEP, positive end expiratory pressure; VAP, ventilator-associated pneumonia; VAC, ventilator-associated complication.

"probable" VAP (Figure 1). There is not a strong correlation between VAE and the older definitions of VAP,[8,9] but VAE is closely associated with patient outcomes, such as length of stay and mortality.[10,11] We sought to determine whether compliance with ventilator bundle practices affects the risk of developing a VAE.

METHODS

We constructed a retrospective cohort study of all adult ventilated patients in the ICUs at Mayo Clinic Rochester between January 2012 and August 2014. The Mayo Clinic Institutional Review Board approved this investigation as a minimal risk study.

We analyzed each episode of ICU admission separately. We excluded patients age <18 years, those who did not have a research authorization on file, those dismissed from the ICU <24 hours after arriving, and those who died within 4 days after ventilator initiation. We excluded the last group because the VAE definition requires the patient be ventilated for ≥2 calendar days to establish a baseline as well as at least 2 days of worsening oxygenation. Thus, the earliest a patient can qualify for a VAE diagnosis is day 4, and records for those expiring before that time are insufficient to classify the occurrence as a VAE versus a non-VAE.[12]

We identified the VAE cases using a database maintained by infection control (IC) personnel for ongoing monitoring activity that uses the CDC/NHSN VAE surveillance algorithm. The IC database used an electronic rule to flag patients who met the criteria for the first tier of VAE, VAC. Infection preventionists reviewed the medical records of all patients who met the VAC criteria to identify the next tiers of VAE and to classify each IVAC case as probable or possible VAE. We considered VAE our primary end point; thus, we removed a patient from the study when an event occurred.

We separately assessed compliance with ventilator bundle elements using an electronic search algorithm to query a database of patient variables in ICUs at our institution.[13] Elements assessed included sedation break, DVT prophylaxis, stress ulcer prophylaxis, and oral care. We elected not to evaluate head-of-bed elevation because chart data were inconsistent.[14]

We assessed compliance with each element in 24-hour windows. An eligible patient was considered to have been "exposed" to a failure the first time when that patient did not have a documented intervention in place. For example, a patient who was on sedation for at least 24 hours was eligible for a sedation break, and if charting failed to note a sedation holiday, we considered this a "failure." For univariate analysis, we carried this onward through the rest of the hospital stay.

We considered DVT prophylaxis compliant if a patient was administered an anticoagulant during that window. This included both therapeutic and prophylactic medications as determined from the medication administration record

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(MAR). We did not allow for exceptions because this was an efficacy study. Although it would be clinically valid to withhold chemoprophylaxis from a patient at risk for bleeding (eg, from a major procedure), the risk of DVT is increased from the day without prophylaxis. We considered peptic ulcer prophylaxis compliant if the patient had any acid inhibitory drug or sulfalcrate on that day charted in the MAR. We evaluated chlorhexidine via the presence of a chlorhexidine in the MAR. Sedation break was assessed only for patients with a continuous IV sedative or opioid present during the window; compliance was considered to have been achieved if that patient had a charted period of at least 15 minutes with all sedatives stopped in the IV fluid administration table. The methods for deriving and validating these definitions are discussed at length elsewhere.[14]

We conducted statistical analyses using JMP 10.0 software (SAS Institute, Cary, NC) and R 3.1.1 (Mavericks, Vienna, Austria). We conducted survival analysis using the R survival package version 2.38.[15] We undertook univariate analysis for compliance with each element by considering VAEs occurring within a 2-day window of failure to meet any ventilator bundle element. We assessed differences in variables between groups using Wilcoxon rank sum, Kruskal-Wallis, or χ^2 test. We used Cox proportional hazard models to assess the effect of stress ulcer prophylaxis, DVT prophylaxis, oral care, and sedation breaks on VAEs. Patients were censored at discharge or death. We adjusted models for gender, age, and Acute Physiology and Chronic Health Evaluation (APACHE) III scores. Because age is a factor in the APACHE III score and, thus, is collinear, we constructed this adjustment with 2 separate models, an age-gender model and a gender-APACHE model. We considered a 2-sided P value $< .05$ statistically significant.

RESULTS

A total of 2,660 patients, comprising 16,858 days at risk, met the inclusion criteria for our study; 77 patients had at least 1 VAE in that period. The median duration of ventilation was 4 days (interquartile range [IQR], 3–7). Median age was 63.9 years (IQR, 53–74 years). The population was predominantly male (61%) (Table 1).

In Table 2, we summarize unadjusted hazard ratios (HRs) for exposure to a bundle element failure. Neither stress ulcer prophylaxis nor DVT prophylaxis nor sedation break were associated with a significant reduction of risk of a VAE. Oral care, however, was statistically significant. Estimating the HR using a multivariate Cox proportional hazard models for all deficiencies in bundle practice for patients at risk of a VAE, the stress ulcer prophylaxis did not attain statistical significance for increased risk of developing VAE. Oral care was again associated with a reduction in VAEs (Table 2).

Constructing a multivariate model and adjusting the significant baseline factors age and gender, we again noted borderline increased risk of VAE from compliance with stress ulcer prophylaxis, significant reductions in VAEs with consistent oral care, and no statistically significant impact of DVT prophylaxis nor sedation breaks. Adjustment for the APACHE score and gender yielded similar results. We excluded 117 patients that did not have an APACHE score calculated from this analysis. The age-gender model and APACHE gender model are provided in Table 3.

TABLE 1. Characteristics of Those With and Without VAE

Variable	VAE Present (n = 77)	VAE Absent (n = 2,583)	P Value
Age, y (range)	62 (49–70)	64 (53–74)	.04
Gender, % male	75	61	.01
Ventilator days (range)	14 (8–24)	4 (3–7)	<.01
APACHE III score (range)	85 (69–100)[a]	84 (66–104)[b]	.60
Hospital LOS, d (range)	30 (18–46)	14 (8–26)	<.01
ICU LOS, d (range)	14 (9–23)	6 (–10)	<.01

NOTE. LOS, length of stay; ICU, intensive care unit.
[a]Missing 2.
[b]Missing 115.

TABLE 2. Risk of VAE With Bundle Elements, Unadjusted

Variable	HR	95% CI	HR (Adjusted)	95% CI
Stress ulcer prophylaxis	1.33	0.84–2.08	1.56	1.00–2.50
DVT prophylaxis	0.91	0.53–1.56	1.03	0.59–1.75
Oral care	0.47	0.28–0.78	0.43	0.25–0.71
Sedation break	0.67	0.37–1.17	0.66	0.38–1.16

NOTE. CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio.

TABLE 3. Adjusted Hazard Ratio for VAE With Bundle Elements

Variable	HR (Adjusted for Age and Gender)	95% CI	HR (Adjusted for APACHE and gender)	95% CI
Stress ulcer prophylaxis	1.56	1.00–2.50	1.59	1.00–2.56
DVT prophylaxis	1.04	0.63–1.79	1.05	0.63–1.81
Oral care	0.41	0.25–0.71	0.44	0.26–0.77
Sedation break	0.71	0.40–1.27	1.50	0.37–1.18

NOTE. CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio.

DISCUSSION

Overall, our findings suggest that while oral care with chlorhexidine appears to be associated with a reduction of VAE, the other bundle elements were not significantly preventive. Sedation breaks and DVT prophylaxis appeared to have no

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overall effect, and stress ulcer prophylaxis may have been trending toward harm.

The value of oral chlorhexidine in preventing VAP is well studied, but results are inconsistent as to who benefits. A recent meta-analysis demonstrated a consistent benefit to oral care with chlorhexidine across 17 published studies,[16] while another found the benefit to be limited only to the cardiac surgery population.[17] In our study, there was a clear benefit, but the study was too small to determine whether these benefits were specific to certain population subsets. The mechanism of oral chlorhexidine for VAP prevention is intuitive. Many VAP organisms are oral flora and may represent some degree of aspiration; thus, reducing the oral bacterial burden should prevent VAP.[18] Of the VAP prevention elements, only head-of-bed elevation and oral care are specifically geared toward infection prevention. The fact that chlorhexidine alone was beneficial in reducing VAEs suggests that infectious events and VAP are still drivers of VAE.

We observed a consistent trend toward harm with stress ulcer prophylaxis. This was not nearly as strong as the benefit seen with chlorhexidine, and it did not ultimately reach significance. This is broadly consistent with other reports questioning the utility of stress ulcer prophylaxis,[19] and the data that stress ulcer prophylaxis may increase the risk of complications, such as *C. difficile*[20] and, depending on the pharmacologic choice, pneumonia.[21] Based on our results, we cannot say that stress ulcer prophylaxis causes harm, but we observed no benefit.

The DVT prophylaxis was not particularly beneficial. This may be because of the relatively short duration of hospitalization (ie, not sufficient time to develop DVT). However, we did not adjust for other known risk factors for DVT (eg, trauma, oncology). It may be that mechanical ventilation alone is not as great a risk factor as other confounders prevalent in this population.

Sedation break trended slightly toward beneficial, but it did not reach statistical significance in any analysis. It is not clear whether this finding is related to the power of our study, though Mehta et al[22] have recently brought the sedation break into question. This finding may reflect study power.

The only nonmodifiable risk factor that was significant was gender. This finding is consistent with prior studies[23] indicating a higher risk of VAP in men. Our study's primary limitation is the low baseline rate of VAE at our institution. With only 77 VAEs for evaluation in this cohort, the strength of any conclusion reached using these data is limited. This low rate further limits generalizability: we did not track other interventions in this study, which may have been responsible for the low rate of VAE and/or may have diluted the impact of traditional bundle elements for prevention.

A specific intervention we could not track was head-of-bed elevation as a bundle element. Our previous validation study did not find reliable enough charting to assess the impact of this intervention. Our definition of noncompliance may also be a limitation; the exact "dose" and window of effect for each intervention are unknown, and our consideration of missing any element for 1 day within a 2-day window of VAE may be too sensitive or specific.

Nonetheless, our study supports the importance of oral care as part of a bundle. Future research should continue to evaluate the role of DVT prophylaxis, sedation breaks, and the potential for harm from stress ulcer prophylaxis. Moreover, other modifiable risk factors such as low tidal volume strategies, glucose control, and early physical therapy should be studied. Non-modifiable risk factors to allow for better targeting of prevention strategies should be further investigated, such as underlying comorbidities and specific ICU population types.

In conclusion, the VAP bundle elements are not well targeted for VAE prevention. Although oral chlorhexidine appears beneficial, other elements had no discernable effect or trend toward increased risk of VAE. If there is a mortality benefit from these interventions, it is not in VAE prevention. Further research is needed to develop a new bundle for the VAE era.

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/ice.2016.207.

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