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Associations Between Ventilator Bundle Components and Outcomes

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IMPORTANCE Ventilator bundles, including head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, thromboprophylaxis, stress ulcer prophylaxis, and oral care with chlorhexidine gluconate, are ubiquitous, but the absolute and relative value of each bundle component is unclear.

OBJECTIVE To evaluate associations between individual and collective ventilator bundle components and ventilator-associated events, time to extubation, ventilator mortality, time to hospital discharge, and hospital death.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included all 5539 consecutive patients who underwent mechanical ventilation for at least 3 days from January 1, 2009, to December 31, 2013, at Brigham and Women's Hospital.

EXPOSURES Head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, thromboprophylaxis, stress ulcer prophylaxis, and oral care with chlorhexidine.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) for ventilator-associated events, extubation alive vs ventilator mortality, and hospital discharge vs hospital death. Effects were modeled using Cox proportional hazards regression and Fine-Gray competing risk models adjusted for patients' demographic characteristics, comorbidities, unit type, severity of illness, recent procedures, process measure contraindications, day-to-day markers of clinical status, and calendar year.

RESULTS Of 5539 consecutive patients undergoing mechanical ventilation, 3208 were male (57.9%), 2331 female (42.1%), and the mean (SD) age was 61.2 (16.1) years. Sedative infusion interruptions were associated with less time to extubation (HR, 1.81; 95% CI, 1.54-2.12; $P < .001$) and a lower hazard for ventilator mortality (HR, 0.51, 95% CI, 0.38-0.68; $P < .001$). Similar associations were found for spontaneous breathing trials (HR for extubation, 2.48; 95% CI 2.23-2.76; $P < .001$; HR for mortality, 0.28; 95% CI, 0.20-0.38; $P = .001$). Spontaneous breathing trials were also associated with lower hazards for ventilator-associated events (HR, 0.55; 95% CI, 0.40-0.76; $P < .001$). Associations with less time to extubation were found for head-of-bed elevation (HR, 1.38, 95% CI, 1.14-1.68; $P = .001$) and thromboembolism prophylaxis (HR, 2.57; 95% CI, 1.80-3.66; $P < .001$) but not ventilator mortality. Oral care with chlorhexidine was associated with an increased risk for ventilator mortality (HR, 1.63; 95% CI, 1.15-2.31; $P = .006$), and stress ulcer prophylaxis was associated with an increased risk for ventilator-associated pneumonia (HR, 7.69; 95% CI, 1.44-41.10; $P = .02$).

CONCLUSIONS AND RELEVANCE Standard ventilator bundle components vary in their associations with patient-centered outcomes. Head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, and thromboembolism prophylaxis appear beneficial, whereas daily oral care with chlorhexidine and stress ulcer prophylaxis may be harmful in some patients.

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Ventilator bundles have been embraced by hospitals around the world to prevent ventilator-associated pneumonia (VAP) and to improve outcomes for patients undergoing mechanical ventilation. Although the precise set of measures included in different hospitals' bundles varies, the Institute for Healthcare Improvement has advocated for a core set of interventions that have been widely adopted by most institutions and tend to make up the core constituents of most hospitals' ventilator bundles.[1-3] These interventions include head-of-bed elevation, daily interruptions of sedative infusions, daily spontaneous breathing trials, thromboembolism prophylaxis, stress ulcer prophylaxis, and oral care with chlorhexidine gluconate.

Many hospitals have reported dramatic reductions in VAP rates after implementing ventilator bundles.[1-9] Interpreting these studies, however, is difficult because VAP is a subjective outcome.[1,10] Lower VAP rates after implementing a bundle may partly reflect stricter application of subjective VAP criteria. Notably, most studies that have reported lower VAP rates after implementing a bundle have not reported parallel decreases in mean duration of mechanical ventilation or mortality.[6]

Furthermore, most ventilator bundle studies have only analyzed bundles as fixed packages rather than disaggregating the positive, negative, or neutral contributions of each bundle component.[2-9] Doing so is important because the data supporting each component are variable and, in some cases, of concern. Data on the association between head-of-bed elevation and VAP, for example, are sparse and inconsistent.[11-13] Some studies[14-16] suggest that stress ulcer prophylaxis may increase the risk of pneumonia among patients with and without ventilation. Oral care with chlorhexidine has been associated with potentially higher mortality rates in 2 meta-analyses of randomized clinical trials.[17,18] Daily interruptions of sedative infusion have been associated with better outcomes in some randomized clinical trials[19,20] but not others.[21] In addition, prior studies on ventilator bundles only considered aggregate monthly adherence rates at the intensive care unit level for all bundle components together rather than taking into account precise day-to-day variations in performance patterns for each bundle component in each patient undergoing mechanical ventilation.

Given these questions, we undertook a detailed analysis of the associations between ventilator bundle adherence practices on a component-by-component, day-by-day basis and their associations with objective outcomes in patients undergoing mechanical ventilation. In particular, we evaluated associations between bundle components and ventilator-associated events (VAEs), duration of mechanical ventilation, ventilator mortality, hospital length of stay, and hospital mortality.

Key Points

Question Are all components of ventilator bundles associated with better outcomes for patients?

Findings Of 5539 patients undergoing mechanical ventilation for at least 3 days, head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, and thromboembolism prophylaxis were associated with less time to extubation alive, whereas oral care with chlorhexidine was associated with an increased hazard for ventilator mortality. Stress ulcer prophylaxis was associated with an increased hazard for ventilator-associated pneumonia.

Meaning Ventilator bundles may merit revision to increase emphasis on beneficial components and to de-emphasize or remove potentially harmful components.

Methods

We conducted a retrospective analysis of prospectively collected data on all patients who underwent mechanical ventilation for at least 3 days in Brigham and Women's Hospital from January 1, 2009, to December 31, 2013. We used operational databases prospectively populated by the hospital's respiratory therapy, nursing, and pharmacy departments to identify patients with mechanical ventilation and to determine which processes of care were performed for each patient for each day of mechanical ventilation. We queried the hospital's Research Patient Data Registry for patients' demographics, encounter dates, laboratory test results, diagnosis codes, and discharge dispositions. We derived patients' comorbidities from diagnosis and diagnosis related group codes using the methods of Elixhauser et al[22] and Charlson et al.[23] We identified VAEs electronically using Centers for Disease Control and Prevention (CDC) criteria, including the subclassifications of infection-related ventilator-associated complications (IVAC) and possible VAP.[24] The study was reviewed and approved by the institutional review board of Partners Healthcare, who granted a waiver of informed consent. This study was conducted under the auspices of the CDC's Prevention Epicenters Program.

Bundle compliance was documented on daily plan sheets kept at each patient's bedside. Examples of these sheets, including instructions and contraindications for each process, are provided in eTable 1 in the Supplement. Bundle compliance was transcribed from these sheets into an electronic database; the sheets were then discarded.

Head-of-bed elevation was assessed by respiratory therapists twice per day and documented as elevated (≥30°), not elevated (<30°), or contraindicated. Sedative infusion interruptions were documented once per day in patients receiving continuous sedative infusions and documented as indicated and performed, contraindicated, or indicated but not performed. We added ventilator-days without continuous sedative infusions to the count of days on which sedative infusion interruptions were indicated and performed to give nurses and physicians credit for avoiding continuous sedative infusions. Spontaneous breathing trials were documented by respiratory therapists as indicated and performed, failed safety screen, or not conducted. Indications and contraindications for sedative infusion interruptions and spontaneous breathing trials mirrored the criteria of Girard and colleagues.[20] Nurses documented thromboembolism prophylaxis daily as indicated and ordered, contraindicated, or indicated but not ordered. Mechanical and/or pharmacologic methods of thromboembolism prophylaxis were eligible; hence, the designation of contraindicated was reserved for patient-days when neither mechanical nor pharma-

cologic methods of prophylaxis were possible. Finally, we queried the electronic medication administration record to determine whether patients received oral care with chlorhexidine and/or stress ulcer prophylaxis daily. Eligible antacids included sucralfate, H_2 blockers, and proton pump inhibitors.

We assessed associations between process measures and VAEs using Cox proportional hazards regression models with fixed and time-varying covariates (eMethods in the Supplement). We censored patients on extubation or death, whichever came first. We assessed the associations between process measures and time to extubation, ventilator mortality, time to hospital discharge, and hospital mortality using Fine-Gray competing risk models to measure the competing risks for extubation alive vs ventilator mortality and hospital discharge alive vs hospital mortality.[25] All models included individual terms for whether or not each process measure was performed on each of the 4 preceding days. We calculated hazard ratios (HRs) for each process measure as the contrast between 4 days of continually performing the process measure vs 4 days of not doing so. We chose a 4-day window to allow for the possibility that process measures might have an immediate and a delayed effect on the probability of an event. For the outcomes of hospital discharge and hospital mortality, we modeled process measure compliance as the cumulative number of days in which each process was performed, and we calculated HRs as the marginal impact of 1 additional day of process measure performance.

We adjusted all analyses for factors that may have affected patients' eligibility for process measures and physicians' readiness to perform them using a combination of fixed and time-varying covariates. We included fixed terms for age, race, sex, unit type (medicine, general surgery, cardiac surgery, cardiac medicine, neuroscience, and thoracic surgery), comorbidities (congestive heart failure, valvular disease, pulmonary vascular disease, chronic lung disease, diabetes, diabetes with complications, renal failure, liver failure, lymphoma, solid cancer, metastases, alcohol abuse, other drug abuse, and psychiatric disease), predicted probability of death on the first day of mechanical ventilation,[26] recent neurosurgery, and recent cardiac surgery. We included time-varying terms for daily sedative exposures (benzodiazepines, propofol, and dexmedetomidine hydrochloride); whether sedative infusions were continuous or intermittent; use of neuroleptics, opioids, neuromuscular blockers, and vasopressors; severe hypoxemia (ratio of Pao_2 to fraction of inspired oxygen, ≤100); and whether a given process measure was marked as contraindicated. We included a term for the calendar year of intubation to adjust for possible temporal changes in practice patterns and outcomes.

We coded each process measure as performed or not performed on each day of mechanical ventilation. If process measure performance was not documented on a given day, we imputed performance or nonperformance by randomly sampling performance data from the same patient from the preceding 4 days. If a value was missing during the first 4 days, we created an initial pool of 4 measurements by simulating 4 independent realizations from a Bernoulli distribution with the probability being the proportion of 1s among all observed daily measures. We repeated the imputation procedure 40 times and combined the 40 effect estimates using the PROC MIANALYZE procedure in SAS (version 9.3; SAS Institute) to obtain an overall effect estimate that took into account within- and between-imputation variations. We also conducted 2 sensitivity analyses wherein all missing processes were set first to *performed* and then to *not performed*.

We evaluated whether performing multiple measures per day conferred additional benefits over performing any single measure alone by tallying the total number of processes performed per day. We restricted this analysis to process measures with evidence of benefit (defined as less time to extubation). We compared the effect of performing 2, 3, or all 4 of these measures per day vs performing 1 or fewer of these measures per day on VAEs, time to extubation, and ventilator mortality. All analyses were performed using SAS (version 9.3).

Results

The study population included 5539 consecutive patients undergoing mechanical ventilation that lasted at least 3 days (3208 male [57.9%] and 2331 female [42.1%]; mean [SD] age, 61.2 [16.1] years). These patients collectively received mechanical ventilation for 48 865 ventilator-days. Patients' characteristics are summarized in **Table 1**. Of 770 VAEs (14 per 100 episodes; 15.8 per 1000 ventilator-days), 313 were IVACs and 197 were possible VAPs. Process measure performance data were complete for 100% of ventilator-days for oral care with chlorhexidine and stress ulcer prophylaxis; 94%, for sedative infusion interruptions; 91%, for head-of-bed elevation; 86%, for thromboprophylaxis; and 82%, for spontaneous breathing trials.

Annual process measure performance rates ranged from 69.6% to 92.5% for head-of-bed elevation, oral care with chlorhexidine, sedative infusion interruptions, stress ulcer prophylaxis, and thromboprophylaxis (**Table 2**). Spontaneous breathing trials, however, were only completed on 24.5% to 32.6% of ventilator-days. Documented contraindications to oral care with chlorhexidine were found for 0.6% of ventilator-days; to stress ulcer prophylaxis, 0.7% of ventilator-days; to thromboembolism prophylaxis, 2.5% of ventilator-days; to spontaneous breathing trials, 7.6% of ventilator-days; to head-of-bed elevation, 7.3% of ventilator-days; and to sedative infusion interruptions, 18.6% of ventilator-days.

Associations between each process measure and VAEs are summarized in **Table 3**. Spontaneous breathing trials were associated with significantly lower hazards for VAEs (HR, 0.55; 95% CI, 0.40-0.76; $P < .001$) and IVACs (HR, 0.60; 95% CI, 0.37-1.00; $P = .05$). Oral care with chlorhexidine was also associated with significantly lower hazards for IVACs (HR, 0.60; 95% CI, 0.36-1.00; $P = .05$) and nonsignificantly lower hazards for VAPs (HR, 0.55; 95% CI, 0.27-1.14; $P = .11$). Stress ulcer prophylaxis, by contrast, was associated with a significantly higher risk for VAP (HR, 7.69; 95% CI, 1.44-41.10; $P = .02$).

Associations between each process measure and other patient outcomes are shown in **Table 4**. Sedative infusion interruptions and spontaneous breathing trials were the most consistently favorable interventions. These 2 processes were

Table 1. Patient Characteristics

Characteristic	No. (%) of Patients (N = 5539)[a]
Age, mean (SD), y	61.2 (16.1)
Sex	
Male	3208 (57.9)
Female	2331 (42.1)
Race	
White	4342 (78.4)
Black	474 (8.6)
Latino	201 (3.6)
Asian	148 (2.7)
Other	374 (6.8)
Intensive care unit type	
Medical	1746 (31.5)
Surgical	1205 (21.8)
Neuroscience	727 (13.1)
Cardiac surgery	668 (12.1)
Cardiac medicine	627 (11.3)
Thoracic surgery	566 (10.2)
Comorbidities	
Coronary artery disease	1203 (21.7)
Congestive heart failure	1217 (22.0)
Peripheral vascular disease	391 (7.1)
Chronic lung disease	643 (11.6)
Diabetes	672 (12.1)
Chronic kidney disease	607 (11.0)
Chronic liver disease	171 (3.1)
Lymphoma	187 (3.4)
Solid malignant neoplasm	872 (15.7)
Alcohol abuse	237 (4.3)
Charlson comorbidity score, mean (SD)[b]	3.6 (2.7)
Ventilator-associated events[c]	770 (13.9)
IVAC[d]	313 (5.7)
Possible VAP	197 (3.6)
Mechanical ventilation-days	
Total No.	48 865
Mean (SD)	8.8 (8.7)
Median (IQR)	6 (4-10)
Hospital length of stay, d	
Mean (SD)	25 (22)
Median (IQR)	20 (12-32)
Hospital mortality	1512 (27.3)

Abbreviations: IQR, interquartile range; IVAC, infection-related ventilator-associated complications; VAP, ventilator-associated pneumonia.

[a] Percentages have been rounded and may not total 100.

[b] Scores range from 0 to 37, with higher scores indicating greater comorbidities.

[c] Includes IVAC and possible VAP.

[d] Includes possible VAP.

associated with increased hazards for extubation (HRs, 1.81 [95% CI, 1.54-2.12; $P < .001$] and 2.48 [95% CI, 2.23-2.76; $P < .001$], respectively), suggesting less time to extubation and hence shorter durations of mechanical ventilation. These processes were also associated with decreased hazards for ventilator mortality (HRs, 0.51 [95% CI, 0.38-0.68; $P < .001$] and 0.28 [95% CI, 0.20-0.38; $P < .001$], respectively). Sedative infusion interruptions were further associated with increased hazards for hospital discharge (HR, 1.09; 95% CI, 1.05-1.14; $P < .001$), suggesting less time to hospital discharge, and lower hazards for hospital mortality (HR, 0.92; 95% CI, 0.88-0.96; $P < .001$). Associations with less time to extubation were found for head-of-bed elevation (HR, 1.38; 95% CI, 1.14-1.68; $P = .001$) and thromboembolism prophylaxis (HR, 2.57; 95% CI, 1.80-3.66; $P < .001$), but these processes had no effect on ventilator mortality, time to hospital discharge, or hospital mortality. Oral care with chlorhexidine, by contrast, did not affect time to extubation but was associated with an increased hazard for ventilator mortality (HR, 1.63; 95% CI, 1.15-2.31; $P = .006$). Stress ulcer prophylaxis also had no effect on ventilator mortality, time to hospital discharge, or hospital mortality. These findings were consistent in the 2 sensitivity analyses in which all missing observations were alternately set to *performed* and then *not performed* (eTable 2 in the Supplement).

Bundling progressively more measures together was associated with exponential increases in HRs for time to extubation alive. We restricted this analysis to the 4 process measures associated with less time to extubation (head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, and thromboembolism prophylaxis) because these processes appeared to have unambiguous evidence of benefit. Performing 2 of these measures per day was associated with an HR for extubation of 2.31 (95% CI, 1.62-3.28; $P < .001$); performing 3 of these measures per day, with an HR for extubation of 3.85 (95% CI, 2.78-5.33; $P < .001$); and performing all 4 measures, with an HR for extubation of 8.77 (95% CI, 6.30-12.22; $P < .001$). Performing all 4 measures was also associated with significantly lower risk for ventilator mortality (HR, 0.14; 95% CI, 0.08-0.25; $P < .001$) but only a nonsignificant decrease in VAEs (HR, 0.59; 95% CI, 0.29-1.19; $P = .14$).

Discussion

The classic ventilator bundle implicitly assigns equal weight to all processes of care by grouping them into a common package and advocating their wholesale implementation. In this large observational cohort, however, we found that the potential risks and benefits of different bundle components vary considerably. Four of the 6 classic ventilator bundle components were associated with positive effects. Head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, and thromboprophylaxis were all associated with less time to extubation and, in the case of sedative infusion interruptions and spontaneous breathing trials, lower rates of ventilator mortality. The 2 other bundle components, however, had no effect on the duration of mechanical ventilation and may have caused some harm. Oral care with chlorhexidine was associated with an increased risk for ventilator mortality, and stress ulcer prophylaxis was associated with an increased risk for possible VAP.

The findings of our study mirror and extend suggestive signals from prior investigations of each bundle component

Table 2. Performance Rates for Processes of Care as a Percentage of Ventilator-days by Year

Process of Care	Year, No. (%) of Ventilator-days				
	2009 (n = 7252)	2010 (n = 11 802)	2011 (n = 10 575)	2012 (n = 9819)	2013 (n = 9417)
Head-of-bed elevation	5185 (71.5)	9460 (80.2)	8717 (82.4)	8322 (84.8)	8088 (85.9)
Oral care with chlorhexidine gluconate	5620 (77.5)	9825 (83.2)	8984 (85.0)	8740 (89.0)	8508 (90.3)
Sedative infusion interruptions[a]	5274 (72.7)	9268 (78.5)	7710 (72.9)	6838 (69.6)	7470 (79.3)
Spontaneous breathing trials	1779 (24.5)	3026 (25.6)	3031 (28.7)	2845 (29.0)	3069 (32.6)
Stress ulcer prophylaxis	6323 (87.2)	10 387 (88.0)	9490 (89.7)	8880 (90.4)	8711 (92.5)
Thromboembolism prophylaxis	5894 (81.3)	10 276 (87.1)	9377 (88.7)	8075 (82.2)	7057 (74.9)

[a] Includes credit for days on which patients were not given continuous sedative infusions.

Table 3. Associations Between Processes of Care and VAEs[a]

Process of Care	HR (95% CI)					
	VAEs	*P* Value	IVACs	*P* Value	Possible VAP	*P* Value
Head-of-bed elevation	1.33 (0.84-2.11)	.23	1.16 (0.59-2.28)	.66	1.60 (0.53-4.88)	.41
Sedative infusion interruptions	0.95 (0.67-1.35)	.76	1.04 (0.61-1.78)	.88	0.82 (0.37-1.82)	.63
Spontaneous breathing trials	0.55 (0.40-0.76)	<.001	0.60 (0.37-1.00)	.05	0.79 (0.39-1.60)	.52
Prophylaxis						
Thromboembolism	0.78 (0.38-1.62)	.51	0.96 (0.26-3.56)	.96	1.13 (0.16-7.78)	.90
Stress ulcer	1.34 (0.87-2.07)	.19	1.62 (0.78-3.35)	.20	7.69 (1.44-41.10)	.02
Oral care with chlorhexidine	0.87 (0.61-1.23)	.42	0.60 (0.36-1.00)	.05	0.55 (0.27-1.14)	.11

Abbreviations: HR, hazard ratio; IVACs, infection-related ventilator-associated complications; VAEs, ventilator-associated events; VAP, ventilator-associated pneumonia.

[a] Includes IVACs and possible VAPs.

Table 4. Associations Between Processes of Care and Patient Outcomes

Process of Care	Outcome, HR (95% CI)							
	Time to Extubation Alive	*P* Value	Ventilator Mortality	*P* Value	Time to Hospital Discharge Alive[a]	*P* Value	Hospital Mortality[a]	*P* Value
Head-of-bed elevation	1.38 (1.14-1.68)	.001	0.86 (0.59-1.25)	.42	1.01 (0.96-1.05)	.80	0.98 (0.93-1.03)	.36
Sedative infusion interruptions	1.81 (1.54-2.12)	<.001	0.51 (0.38-0.68)	<.001	1.09 (1.05-1.14)	<.001	0.92 (0.88-0.96)	<.001
Spontaneous breathing trials	2.48 (2.23-2.76)	<.001	0.28 (0.20-0.38)	<.001	1.00 (0.98-1.02)	.92	0.99 (0.96-1.02)	.46
Prophylaxis								
Thromboembolism	2.57 (1.80-3.66)	<.001	1.39 (0.82-2.37)	.23	1.02 (0.97-1.07)	.41	0.97 (0.92-1.02)	.26
Stress ulcer	1.12 (0.95-1.32)	.17	0.91 (0.64-1.31)	.62	1.00 (0.98-1.03)	.89	1.00 (0.96-1.04)	.90
Oral care with chlorhexidine	0.92 (0.80-1.04)	.18	1.63 (1.15-2.31)	.006	0.99 (0.98-1.01)	.26	1.01 (0.98-1.05)	.44

Abbreviation: HR, hazard ratio.

[a] Analyses are restricted to patients who survived mechanical ventilation.

in isolation. The strong associations between sedative infusion interruptions and spontaneous breathing trials and less time to extubation parallel the findings of multiple randomized clinical trials[19,20,27,28] and prospective quality improvement initiatives that have also reported associations between these interventions and shorter ventilator stays.[29] The present study extends these trials by suggesting that these interventions may also confer a mortality benefit.

Our finding that head-of-bed elevation is associated with shorter ventilator stays is useful affirmation that this practice is indeed beneficial for patients. Almost 99% of US hospitals report routinely placing patients undergoing ventilation in the semirecumbent position.[30] The evidence of benefit, however, is sparse. Only 3 randomized clinical trials[11-13] with a combined enrollment of 337 patients have evaluated the effect of head-of-bed elevation on VAP rates. One small trial reported a significant decrease.[11] The second trial did not find lower VAP rates, but the rate of adherence to head-of-bed elevation was very low.[12] The third trial reported a nonsignificant decrease in VAPs but was underpowered.[13] None of these trials were adequately powered to assess for changes in duration of mechanical ventilation or other objective outcomes. Our study suggests that elevating the head of the bed may decrease time to extubation.

Likewise, the favorable association between thromboprophylaxis and time to extubation further affirms the utility of this practice in populations undergoing mechanical ventilation. Randomized clinical trials[31] have demonstrated that thromboprophylaxis lowers the incidence of thromboemobolic disease in critically ill patients, and 1 large observational series[32] suggested that delayed initiation of thromboprophylaxis increases mortality risk.

The paradoxical association between oral care with chlorhexidine and lower rates of IVACs and VAP but higher mortality rates parallels the findings of 2 recent meta-analyses of randomized clinical trials.[17,18] These meta-analyses also reported that oral care with chlorhexidine was associated with lower VAP rates but potentially higher mortality rates. The reason for the possible increase in mortality risk is not clear. The authors of 1 of the meta-analyses[18] speculated that some patients may aspirate some chlorhexidine, leading to acute lung injury in a fraction of patients.

Data on the association between stress ulcer prophylaxis and nosocomial pneumonia are inconsistent.[33] Nonetheless, multiple studies[14-16] have reported associations between stress ulcer prophylaxis and increased risk for pneumonia, particularly with proton pump inhibitors. The risk for pneumonia appears to be particularly pronounced in patients receiving enteral nutrition.[34] Our study further raises the concern that stress ulcer prophylaxis may increase the risk for VAP in some patients, although the confidence interval for our estimate was wide.

The findings of this study need to be interpreted with caution. This study was observational rather than a randomized clinical trial. Therefore, some of the observed associations between different processes of care and various outcomes may better reflect patients' underlying medical conditions and the reasons that various processes were performed or not performed (ie, these patients' eligibility for a specific process rather than the effect of the process). This difference is a particular concern for spontaneous breathing trials, given that they were only performed on a fraction of ventilator-days. We adjusted our analyses for an extensive array of factors, however, to account for patients' baseline mortality risk, comorbidities, recent procedures, location of care, and multiple indicators of daily clinical status (including the need for vasopressors, severe oxygen impairment, use of neuromuscular blockers, sedative exposures, and whether the nurses and/or physicians documented a contraindication to each particular process measure). Furthermore, we found that some ventilator bundle components were associated with deleterious outcomes, making it unlikely that process measure performance alone is merely a proxy for better health. Finally, the pattern of positive and negative associations between different processes mirrors the findings of randomized clinical trials of each process in isolation.

Other limitations of our study include missing data for some processes. Our results did not change, however, when we conducted 2 sensitivity analyses that alternately set all missing observations to *performed* and then *not performed*. This finding suggests that the overall quantity of missing data was small and did not influence the final results. Last, the findings of this single-center study in a tertiary care hospital may not be generalizable to other settings.

Conclusions

We found that ventilator bundle components differ in their associations with VAEs, duration of mechanical ventilation, and other outcomes. Sedative infusion interruptions and spontaneous breathing trials were associated with less time to extubation and lower rates of ventilator mortality. Head-of-bed elevation and thromboprophylaxis were associated with less time to extubation. Oral care with chlorhexidine and stress ulcer prophylaxis, by contrast, did not affect the duration of mechanical ventilation and were associated with an increased risk for ventilator mortality and possible VAP, respectively.

These findings suggest that we should revisit the classic ventilator bundle. Possible revisions include increasing the emphasis on maximizing sedative infusion interruptions and spontaneous breathing trials, a reappraisal of whether oral care protocols should be revised to exclude chlorhexidine therapy, and the reservation of stress ulcer prophylaxis for patients at marked and immediate risk for upper gastrointestinal tract bleeding rather than prescribing them for all patients undergoing ventilation. In addition, some interventions from outside the classic ventilator bundle might further benefit patients undergoing ventilation such as low tidal volume ventilation, conservative fluid management, and early mobilization.[35-38] New and better ventilator bundles that integrate these promising new processes with the best components of traditional ventilator bundles are needed.

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Study concept and design: Klompas, Massaro.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Klompas.
Critical revision of the manuscript for important intellectual content: All authors.
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