Ventilator Bundles in Transition: From Prevention of Ventilator-Associated Pneumonia to Prevention of Ventilator-Associated Events

Richard H Kallet

Implementation of ventilator bundles is associated with reductions in ventilator-associated pneumonia (VAP). However, the new surveillance model of ventilator-associated events (VAEs) has shifted the focus from VAP to objective, generalized signs of pulmonary decompensation not specific to VAP. This raises the question of whether the ventilator bundle also is effective in reducing VAE. This narrative review examined 6 studies published since 2013 that assessed the impact of ventilator bundles on the incidence of VAE, and a seventh study that examined its impact on mortality. All 7 studies were low-level evidence, and only 1 study was prospective. The findings among the studies were inconsistent, and the only prospective study found no difference in bundle adherence between those who did and did not develop VAE. However numerous factors may explain the apparent lack of efficacy. Most of these factors were related to the retrospective nature of the studies, such as suboptimal documentation of bundle procedures and the presence of potential non-modifiable risk factors, as well as insufficient performance of most bundle components. In some studies, low VAE incidence also raised uncertainty about the veracity of results. Despite these limitations, there was evidence suggesting that stress ulcer prophylaxis may increase VAE risk, and oral care with chlorhexidine may increase both VAE and mortality risk. The largest study found significant reductions in duration of intubation with weaning, sedation, and head of bed elevation, as well as reduced mortality risk with weaning and sedation bundle elements. Nonetheless, these studies should be useful in designing future prospective controlled studies to determine what elements of a future prevention bundle might be effective in reducing VAEs. At this juncture, and based on the limited evidence to date, it appears that incorporating daily sedation interruptions and spontaneous breathing trials are the factors most likely to reduce VAEs. Key words: ventilator-associated pneumonia; ventilator-associated events; ventilator-associated conditions; infection-related ventilator-associated complications; ventilator bundle. [Respir Care 2019;64(8):994–1006. © 2019 Daedalus Enterprises]

Introduction

Reducing hospital-acquired infections is at the forefront of efforts to improve patient-centered outcomes and to reduce health care expenditures by monitoring hospitals for preventable complications. An early initiative involved standardizing evidence-based practices that reduce ventilator-associated pneumonia (VAP) into a package generically referred to as a “ventilator bundle.”¹ These endeavors

consequently brought to the forefront some inherent limitations in the diagnosis of VAP.

In 2011, the Department of Health and Human Services enlisted help from the Centers for Disease Control and Prevention, the Critical Care Society Collaborative

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Mr Kallet is an Associate Editor for RESPIRATORY CARE.

Mr Kallet discloses a relationship with the Asthma and Allergy Prevention Company.

Mr Kallet presented a version of this paper at the New Horizons Symposium: Ventilator-Associated Events-Surveillance and Understanding at the AARC Congress 2018, held December 4-7, 2018, in Las Vegas, Nevada.

Correspondence: Richard H Kallet MSc RRT FAARC. E-mail: richkallet@gmail.com.

DOI: 10.4187/respcare.06966

Table 1. Elements of a Ventilator Bundle Used to Reduce Incidence of VAP

Element	Rationale for Preventing VAP
Head of bed elevation: 30–45°	Reduce the potential for gastric reflux and aspiration of contaminated orogastric secretions
Avoidance of nasogastric tubes, limiting the use of orogastric tubes	Reduce upper airway contamination by preventing sinus infections and/or improve lower esophageal sphincter competency through the absence of foreign objects and ease of gastric fluid/bacterial migration via an open pathway up the esophagus
Oral care with chlorhexidine	PVC materials used in catheters facilitates bacterial growth Reduce the introduction and load of potentially pathogenic microbes into the oropharynx and, by extension, colonization of the lower respiratory tract
Protective cover for oral (“tonsil-tip”) suction devices when not in use	Protective covers reduce the risk of introducing potentially pathogenic bacteria into the oropharynx
Spontaneous breathing trial	Reduce exposure to mechanical ventilation
Daily sedation interruption	Reduce exposure to mechanical ventilation
Deep vein thrombosis prophylaxis	Extraneous to VAP prevention
Stress ulcer prophylaxis	Extraneous to VAP per se*
Specially designed ETT and associated devices	Reduction of secretions pooled above the ETT cuff
ETT with subglottic drainage	Reduction of secretion seepage around or through microchannels in the ETT
Silver-coated ETT, ETT with tapered cuff design, or ETT made with polyurethane material (vs PVC material)	Reduction of microbes in biofilm residing in the ETT lumen
Special catheter to remove biofilm from the ETT lumen	Mechanical removal of contaminated biofilm from the ETT lumen
Automated monitoring and control of ETT cuff pressure to prevent gross aspiration and limit the degree of microaspiration of orogastric secretions	Reduce contamination of the ventilator circuit
Ventilator circuit-related	
Circuit replacement weekly or when visibly soiled	Reduce contamination of the ventilator circuit
Closed suction catheters as part of the ventilator circuit with the same replacement regimen	Reduce the risk of microaspiration that occurs with either the abrupt loss of PEEP (during circuit disconnect) and perturbation of the ETT cuff
Use of heat-moisture exchangers	
Protective covers for both self-inflating resuscitation bags	
Hand hygiene before and after contact with the ventilator or ventilator circuit	

* Proton pump inhibitors increase gastric pH and facilitate bacterial growth that enhances bacterial load of gastric fluids. Prophylaxis with sucralfate recommended (ie. does not raise gastric pH).
VAP = ventilator-associated pneumonia
ETT = endotracheal tube
PVC = polyvinyl chloride

Group, and Infectious Disease Societies to develop a more credible VAP definition to monitor hospital performance.² The result was our current ventilator-associated events (VAEs) model,³ which shifted the emphasis of surveillance monitoring from VAP to secondary pulmonary complications arising in mechanically ventilated patients.

This narrative review examines whether ventilator bundles designed to reduce VAP remain relevant in the VAE era. It will begin by examining the rationale and evidence upon which various bundle components are based. It provide a brief description of the VAE model, review studies that examined the impact of VAP ventilator bundles on VAE, and evaluate how new iterations of ventilator bundles might reduce VAEs.

The Generic Ventilator Bundle

Ventilator bundles are standardized practices based upon evidence of varying quality.⁴ Although they differ in components, most include core practices such as semi-recumbent positioning, oral care, avoidance of nasogastric tubes, limited use of orogastric tubes, and strategies to limit the duration of mechanical ventilation by incorporating daily sedation interruptions (DSI) and spontaneous breathing trials (SBT) (Table 1). Some bundles include specialized endotracheal tube(s) (ETT) with subglottic suctioning and/or modified cuff design to reduce microaspiration of orogastric secretions or “closed” ETT suction systems, and protocols to reduce or eliminate routine ventilator circuit changes. Although often not explicitly stated, ventilator

bundles assume strict adherence to hand hygiene. Finally, while seemingly unrelated to VAP, ventilator bundles also have included standardized practices for prophylaxis of stress ulcers and deep vein thrombosis.

Patient Positioning

Gastroesophageal reflux is related to frequent occurrences of lower esophageal sphincter relaxation and commonly occurs while supine.⁵ Positive pressure gradients between the gastric and esophageal compartments (ie, intra-abdominal vs intrathoracic) facilitate reflux that is magnified further by gastric distention,⁶ compression by abdominal viscera,⁷ and intra-abdominal hypertension.⁸ Regardless of size, the presence of any gastric tube enhances reflux by stenting open the lower esophageal sphincter.⁹

In the past, mechanically ventilated patients often were kept supine and frequently had nasogastric tubes in place. A seminal study found that this was associated with higher incidences of orogastric secretion aspiration, microbial colonization, and VAP compared to semi-recumbent positioning at a 45° angle.^{10,11} Enteral feedings also are associated with VAP,¹² such that being in the supine position while feeding magnifies the incidence of VAP.¹⁰ Yet, sustained positioning at 45° was found impractical compared to positioning at 25–30°.⁹ In addition, nasogastric tubes are associated with sinusitis,¹³ and this is enhanced substantially when an ETT is present.^{14,15} Sinusitis itself substantially increases the risk of VAP (odds ratio 3.66 [interquartile range (IQR) 1.81–7.37]).¹⁵

The most recent systematic review comparing supine positioning with semi-recumbent positioning found no difference in clinically suspected or microbiologically confirmed VAP between positioning at 45° versus 25–30° (relative risk 0.74 [IQR 0.35–1.56] and 0.61 [IQR 0.20–1.84], respectively).¹⁶ Although inter-study heterogeneity and bias risk found in this study (as well as another systematic review)¹⁷ do not provide a conclusive answer, it is apparent that, unless contraindicated, all patients should be positioned semi-recumbent at ≥ 25°.

An alternative strategy to reduce VAP is placing patients in the lateral horizontal position.¹⁸ This reduces microaspiration by limiting pooling above the ETT cuff and removes gravitational forces favoring distal migration of any aspirated secretions. A variation of this technique is adding Trendelenburg positioning to enhance secretion movement cephalad.

Two preclinical trials of lateral horizontal-Trendelenburg position found reduced bacterial counts both in the ETT and lower airways compared to the head-up position,¹⁹ and zero versus 75% incidence of pneumonia, respectively ($P = .007$).²⁰ In a small clinical trial, pepsin levels in tracheal aspirates, which is a signifier for aspi-

ration of orogastric secretions, were not different between subjects positioned lateral horizontal versus semi-recumbent at ≥ 30°.¹⁸ A large prospective, multi-center, randomized controlled trial (RCT) found that lateral horizontal-Trendelenburg position reduced VAP compared to semi-recumbent position (0.05% vs 4.0%, $P = .04$). However, the study was terminated early for poor enrollment due to low incidence of VAP. Moreover, the lateral horizontal-Trendelenburg position was associated with serious adverse events compared to semi-recumbent positioning (6% vs 0%, $P = .01$).²¹

Therefore, current evidence suggests no advantage but indicates increased risk of adverse effects with lateral horizontal positioning versus semi-recumbent positioning without further benefit in reducing VAP.

ETT Design and Related Ancillary Practices

Modified ETT designs and ancillary techniques are used to prevent microaspiration of orogastric secretions around the ETT cuff, to prevent bacterial colonization of the ETT, to remove pathogenic biofilm from the ETT lumen, and to regulate ETT cuff pressure. The pathophysiologic rationale is that VAP emanates either from chronic microaspiration of secretions pooled above the ETT cuff²² or from pathogenic organisms in biofilm that accumulates inside the ETT.²³

Pooled subglottic secretions cannot be removed by suctioning the oral cavity. To adequately seal the airway, polyvinyl chloride ETT cuffs require a diameter greater than the trachea.²⁴ This interface mismatch between cuff and tracheal wall forms longitudinal folds or “micro-channels” that facilitate seepage of infected orogastric secretions into the lungs.²⁵ Evacuating subglottic secretions require specialized ETTs with an imbedded suction channel terminating above the cuff. Several meta-analyses of RCTs testing subglottic drainage ETTs found a substantial reduction in VAP ranging between 42–54%.^{26–28}

ETT cuffs made with thin polyurethane form fewer microchannels and appear to perform better in preventing fluid leakage.²⁹ ETTs with tapered or conical cuffs conform better with the shape of the trachea and can reduce microaspiration.³⁰ However, despite laboratory studies demonstrating reduced leakage with polyurethane cuffs, this has not necessarily reduced VAP risk.^{31,32} Likewise, tapered and conical cuffs have not reduced VAP compared to standard ETT cuffs.³¹

Under-inflated ETT cuffs producing insufficient cuff pressures (ie, ≤ 20 cm H₂O) are independently associated with VAP.³³ In relatively small, single-center trials, continuous control of cuff pressures between 20–30 cm H₂O reduced VAP by approximately 50–60%.^{33,34} Currently, 2 large, multi-center RCTs are underway to examine

whether continuous versus intermittent monitoring and control of ETT cuff pressure reduces VAP.^{35,36}

Colonization (particularly by multi-drug resistant pathogens) of biofilm in the ETT lumen is another source of VAP. Two strategies that address this problem are preventing colonization by impregnating ETTs with silver or other antimicrobial agents, or by periodically removing biofilm from the internal lumen of the ETT with a scraping device.

Silver possesses broad-spectrum antimicrobial properties when nanoparticles are incorporated into various medical products.³⁷ The bactericidal mechanism is the slow release of silver cations that disrupt bacterial cell walls. A systematic review found that silver-coated ETTs significantly reduced VAP risk (relative risk 0.64 [IQR 0.43–0.96]) and delayed onset of VAP (hazard ratio 0.55 [IQR 0.37–0.84]).³⁸

Removing biofilm from the ETT was introduced in 2005,³⁹ and a subsequent small study reported lower bacterial colonization compared to that found with usual care practice (8% vs 83% respectively, $P < .001$).⁴⁰ However, a larger study found no difference in bacterial counts between routinely cleaned ETTs versus usual care practices.⁴¹ To date, no studies have demonstrated that removing biofilm reduces the incidence of VAP.

In summary, strong evidence supports subglottic drainage to reduce VAP, whereas compelling evidence for using ETT cuffs made with altered shapes or materials is lacking. Continuous monitoring and control of ETT cuff pressure to reduce VAP awaits results from ongoing large RCTs. Silver-coated ETTs appear to reduce the incidence of VAP, whereas evidence to support biofilm removal from the ETT to reduce VAP currently is lacking.

Reducing the Duration of Mechanical Ventilation

VAP risk rises with increasing mechanical ventilation duration.⁴² The majority of VAP cases (62–73%) are “late onset” (ie, occurring at > 4 d), with the highest risk occurring between days 6 and 8.⁴ Thus, identifying patients early who no longer need mechanical ventilation may reduce VAP. Strategies that might accomplish this are restricting sedative use (ie, DSI or targeted light sedation practices),^{43,44} and either SBT⁴⁵ or early extubation to noninvasive ventilation in select patients.⁴⁶

Historically, 40–50% of mechanical ventilation duration was devoted to weaning.⁴⁷ Studies from the mid- to late 1990s reported traditional weaning practices added 5.7 ± 3.7 to 9.3 ± 8 d compared to SBT.⁴⁸ Approximately 80% of subjects passed their initial SBT, and only 13% failed subsequent extubation within 48 h.⁴⁷ SBT reduced weaning by 1–2 d⁴⁹ and mechanical ventilation by 1.5 d compared to usual care practices.⁵⁰ Likewise, DSI reduced median mechanical ventilation by 2.4 d,⁴⁴ whereas tar-

geted light sedation decreased it by 1.2–2.6 d.⁵¹ Combining SBT with DSI increased mean ventilator-free days by 3.1 d.⁴³

Nonetheless, evidence regarding the impact of DSI and SBT on VAP is scant, and when reported it mostly comes from studies in which VAP was a secondary outcome. Only a small RCT of DSI versus usual care used VAP as a primary end point.⁵² By study day 5, the incidence of VAP was lower in subjects treated with DSI compared to those treated with usual care (27.5% vs 55.3% respectively, $P < .05$). A prospective time-series study of a sedation protocol was associated with reduced median mechanical ventilation duration (4.2 d [IQR 2.1–9.5] vs 8.0 [IQR 2.2–22.0] d, $P = .001$) and VAP (hazard ratio 0.81 [IQR 0.62–0.95], $P = .03$) compared to physician-directed practice.⁵³ A post hoc analysis of the seminal DSI study⁴⁴ found median mechanical ventilation duration was lower in subjects randomized to DSI versus usual care practices (4.8 [IQR 2.9–8.0] vs 7.3 [IQR 3.4–16.1] d, respectively, $P = .003$).⁵⁴ However, VAP incidences between the 2 treatment arms (3.0% vs 8.3%, respectively) were not significant (odds ratio 0.34 [IQR 0.06–1.84], $P = .26$).

The only large RCT of SBT weaning that reported VAP found a trend toward reduced VAP only in trauma-surgical subjects (6% vs 19% in the control arm, $P = .061$) and no discernable impact in medical subjects.⁵⁵ This occurred despite a significant decrease in median mechanical ventilation (2.8 vs 5.2 d in the control arm, $P < .001$). A large time-series study of an SBT weaning protocol found that mechanical ventilation duration and VAP cases had decreased between the pre- and post-implementation periods (5.0 ± 4.3 vs 3.0 ± 4.7 d, $P < .001$; and 15% vs 5%, $P < .001$, respectively).⁵⁶

In a prospective study of early extubation to noninvasive ventilation versus traditional weaning and extubation practices, early extubation was associated with reduced mechanical ventilation duration (4.0 [IQR 3.0–7.0] d vs 5.5 [IQR 4.0–9.0] d, respectively, $P = .004$) and lower incidences of VAP and ventilator-associated tracheobronchitis (9% vs 25% respectively, $P = .02$).⁵⁷

In summary, DSI and SBT protocols substantially reduce mechanical ventilation duration, but not necessarily VAP. This likely reflects the confounding influence of “early-onset” VAP (ie, 48–96 h after intubation), which represents 25–40% of all cases. Without a well-designed and sufficiently powered RCT with VAP as the primary outcome, the ability to control or account for non-modifiable risk factors (eg, poor dental health, malnutrition, trauma, ARDS, chronic heart or renal failure, and acute multi-organ failure)^{4,58} will stymie our ability to ascertain whether these practice improvements actually reduce incidence of VAP.

Ancillary Respiratory Care Practices

In 1965, the term “respirator lung” described ventilator-acquired, (predominantly) Gram-negative bronchopneumonia. This often progressed to intractable respiratory failure⁵⁹; this was soon recognized as ARDS.⁶⁰ Infection-control deficiencies were identified as likely sources, including non-sterile suction technique and supplies, non-sterilized ventilator circuits, and condensation build-up in ventilator hoses. Correcting these deficiencies (including sterilized ventilator circuits with frequent changes) reportedly eliminated the syndrome.

Beginning in the mid-1980s, the relationship between ventilator circuit and suctioning practices and VAP were again examined.⁶¹ Reducing circuit changes from every 24 h to every 48 h reduced VAP by 50% ($P = .02$),⁶² while reductions from every 48 h to every 7 d either reduced VAP risk further⁶³ or had no impact.⁶⁴ In addition, not changing the ventilation circuit altogether (unless it was visibly soiled) had no impact on VAP compared to routine changes every 7 d.^{65,66}

Heat-moisture exchangers (“passive humidification”) and heated wire circuits for “active humidification” were designed to reduce bacterial colonization by eliminating condensation within the circuit.^{61,67} Although ventilator circuits typically are contaminated by the same organisms colonizing the patient’s lungs,⁶⁸ condensation nevertheless provides a medium for bacterial growth. Unaffected by antibiotic therapy this microbial reservoir is a persistent source for pulmonary reinoculation. However, convincing evidence that these strategies are superior to active humidification alone in reducing VAP remains elusive.⁶⁷⁻⁷⁰

Open endotracheal suctioning may cause VAP as disconnecting the circuit increases the risk of inadvertent contamination as it (or the manual resuscitator) often comes into contact with the bed; or the ETT may become colonized accidentally by a contaminated suction catheter.⁷¹ Closed catheter systems obviate these potential sources. Although closed systems are at higher risk for bacterial contamination (typically by the patient’s infected secretions)⁶⁸ than open systems,⁷²⁻⁷⁴ this has not translate into increased VAP risk.⁷²⁻⁷⁶

Oral Care

During critical illness, the stomach often becomes colonized with Gram-negative bacteria.⁷⁷ Frequent gastroesophageal reflux causes the oral cavity to be colonized with these and other pathogenic microorganisms (eg, *Streptococcus* species, *Candida albicans*). In VAP, the same bacteria often are isolated from both the oral cavity and sputum.⁷⁷⁻⁸⁰ In addition, preexisting dental disease is associated with both community-acquired and hospital-acquired pneumonia.⁸¹

Oral care practices for VAP prophylaxis include oral swabs, tooth brushing, and rinses with normal saline, povidone iodine, or chlorhexidine. In systematic reviews, oral care with chlorhexidine solution or gel reduces VAP risk by 25% to 40%, with uncertain or no additional benefit from augmenting oral care with tooth brushing.^{82,83}

Hand Hygiene

Several time-series studies underscore the importance of hand hygiene in reducing VAP. Of these, Rello et al⁶⁵ reported reduced VAP risk (odds ratio 0.35 [IQR 0.11–0.68]. Introducing oral care and hand hygiene measures alone reduced early-onset VAP by 59% and was inversely proportional to clinician compliance.⁸⁴ Body-worn hand gel devices reduced VAP from 6.9 cases/1,000 d to 3.7 cases/1,000 d of mechanical ventilation ($P < .1$).⁸⁵ In another study, hand hygiene alone reduced all respiratory tract infections by 36.3 infections/1,000 device days.⁸⁶

Stress Ulcer and Deep Vein Thrombosis Prophylaxis and VAP

Critical illness increases the risk for stress ulcers and deep vein thrombosis. Prophylaxis for each is included in ventilator bundles despite no direct association with VAP risk. Most drugs used for stress ulcer prophylaxis reduce gastrointestinal bleeding by increasing gastric pH.⁸⁷ However, this promotes bacterial colonization and is associated with increased VAP risk.^{88,89} Therefore, VAP prophylaxis has recommended sucralfate because it does not increase gastric pH.⁹⁰ Despite its greater effectiveness in reducing VAP compared to other agents, sucralfate is less effective in reducing gastrointestinal bleeding.⁸⁸

These unrelated prophylactic therapies likely were included in the ventilator bundle to promote sucralfate in reducing VAP risk; whereas their inclusion also was likely viewed as an opportunity to expand the scope of bundled therapies to reduce overall morbidity and mortality. And now the VAE model, with its shifting emphasis from VAP to generalized deterioration in pulmonary function associated with mechanical ventilation, may present another opportunity for improving and monitoring critical care practices that might enhance patient-centered outcomes.

The VAE Model

In the VAE model, VAP is delimited to patients whose oxygenation is stable or improving over a 2-d period, who then experience sustained deterioration (Table 2). The initial criterion, ventilator-associated condition (VAC), is based on reasonable thresholds for escalating F_{IO_2} or PEEP, which in turn is sustained for an additional 2 d. These prerequisites hypothetically filter out transient oxygenation

Table 2. The VAE Model and Its Relationship to VAP

Step	Name	Category and Implication	Criteria
1	Baseline period	None	≥ 2 d of sustained mechanical ventilation characterized as stable or improving oxygenation, specifically no increase in either the <i>minimum</i> F _{IO₂} or PEEP in the 2 d prior to deterioration in oxygenation.
2	VAC	VAE; potentially publicly reportable event	On or after day 3: the required <i>minimum settings</i> to maintain adequate oxygenation increases for F _{IO₂} ≥ 0.20 and/or PEEP ≥ 3 cm H ₂ O Sustained increase for additional 2 d
3	IVAC	VAE; potentially publicly reportable event	On or after day 3: deterioration in oxygenation also is associated with signs of infection: Temperature < 36°C or > 38°C or WBC < 4 or > 12 × 10 ³ cells/mm ³ Initiation or additional antibiotic therapy with ± 2 d of VAC Antibiotic therapy sustained for > 4 qualifying antimicrobial days
4	Possible VAP	Internal infection control and/or quality assurance monitoring	On or after day 3: IVAC and one of the following: Positive culture indicating a potentially pathogenic organism ≤ 2 calendar days before or after VAC onset* + culture meeting quantitative or corresponding semi-quantitative threshold for endotracheal aspirate (≥ 10 ⁵ CFU/mL), BAL fluid or lung tissue (≥ 10 ⁴ CFU/mL), or PSB (≥ 10 ³ CFU/mL). Purulent secretions defined as emanating from lungs containing ≥ 25 neutrophils and ≤ 10 epithelial cells per low-power field (×1,000) and organisms identified from the specimens listed above. Positive test results for an organism identified from pleural fluid (via thoracentesis), lung histopathology, or <i>Legionella</i> species or viruses (eg, parainfluenza, respiratory syncytial virus).

* Excluding the first 2 d of mechanical ventilation.

VAP = ventilator-associated pneumonia

VAE = ventilator-associated events

VAC = ventilator-associated complication

IVAC = infection-related ventilator-associated complication

WBC = white blood cell count

CFU = colony-forming unit

BAL = bronchoalveolar lavage fluid

PSB = protected specimen brush

problems caused by readily reversible, non-infectious sources (eg, atelectasis, fluid overload, mucus plugging).

The second criterion, infection-related ventilator-associated complication (IVAC), occurs when VAC coincides with quantifiable signs of infection. Both VAC and IVAC constitute a VAE. Surveillance criteria for VAP are met only when IVAC criteria coincides with sputum or bronchoalveolar fluid samples meeting thresholds for neutrophils and positive cultures for potentially pathogenic organisms. Originally distinguished into “possible” or “probable” VAP (based on culture technique), they were later simplified as “possible VAP” (PVAP).⁹¹

At some point, VAE surveillance (excluding VAP) may be used for public reporting.⁹² The shift in focus to deteriorating lung function in mechanically ventilated patients was intended to make VAE surveillance as objective as

possible, so as to facilitate automation and improve comparability between institutions.⁹³ When coupled with severity of illness scores, tracking VAE might allow for credible risk adjustments when hospitals are benchmarked against one another.⁹³

Ventilator Bundle Impact on VAE

To date, 6 studies⁹⁴⁻⁹⁹ have examined the impact of ventilator bundles on VAE; of these, 5 were retrospective studies (Table 3). A recent meta-analysis examined the impact of ventilator bundles on mortality.¹⁰⁰ Initial studies (in 2013–2014)⁹⁴⁻⁹⁶ focused primarily on the relationship between VAC, IVAC, and VAP, not the impact of ventilator bundles on VAE. These studies had 4 common

VENTILATOR BUNDLES IN TRANSITION

Table 3. Impact of the Ventilator Bundle on VAE Incidence

Study/Design Setting and Objective(s)	Bundle Characteristics	Major Findings
Ding et al 2013 ⁹⁴	DSI	Formal adoption of a ventilator bundle did not impact the incidence of VAC, IVAC, or VAE-VAP
Retrospective, single-center, time-series study	Oral care with chlorhexidine	Potential explanations include:
All adults undergoing mechanical ventilation for ≥ 48 h over 72 months	HOB elevation	Very low pre-post incidence of VAE: VAC (11% vs 11%), IVAC (3% vs 4%), and probable or possible VAP (1% vs 4%)
$N = 684$ subjects	SBT	Bundle adherence is unknown because ventilator bundle components (eg, SBT and DSI) were already used ad hoc during the pre-implementation period, albeit with inadequate documentation
The incidence and outcome of VAP (using multiple definitions including VAE) before and after introduction of the ventilator bundle	Stress ulcer prophylaxis	
Muscudere et al 2013 ⁹⁵	DSI	Increased bundle compliance associated with decreased incidence of VAC but not IVAC
Retrospective, multi-center, time-series study	Oral care with chlorhexidine	Over 24-month study period, adherence with several elements improved substantially but likely insufficiently for accurate assessment of the full potential for prophylaxis (eg, HOB elevation increased from 29% to 41%; oral care with chlorhexidine increased from 16% to 50%, SSD increased from 36% to 58%)
11 North American adult ICUs over 24 months	HOB elevation	There was a trend toward decreased incidence of VAC and IVAC associated with an increased % of days with DSI and SBT performed
$N = 1,320$ subjects	SBT	DSI: OR 0.93 (IQR 0.87–1.00), $P = .05$
To assess the impact of the ventilator bundle on incidence of VAE	SSD	SBT: OR 0.97 (IQR 0.94–1.01), $P = .10$
		Subjects with either VAC or IVAC tended to have undergone nasotracheal intubation
Lewis et al 2014 ⁹⁶	DSI	Multivariate logistic regression modeling revealed that none of the bundle elements was associated with either VAC or IVAC
Retrospective single-center case-control study	DVT prophylaxis	The relationship between positive fluid balance (per L) and VAC approached significance: OR 1.2 (IQR 1.0–1.4)
All ICUs studied over a 12-month period	Oral care with chlorhexidine	
$N = 220$ subjects (100 case subjects; 110 control subjects)	HOB elevation	
To identify risk factors for VAC and IVAC	Stress ulcer prophylaxis	
	SBT	
Klompas et al 2016 ⁹⁷	DSI	DSI associated with:
Retrospective, single-center, observational cohort study	DVT prophylaxis	Decreased time to extubation: hazard ratio 1.81 (IQR 1.54–2.12), $P < .001$
All subjects undergoing mechanical ventilation for > 3 d over 48 months	Oral care with chlorhexidine	Decreased mortality risk during mechanical ventilation: hazard ratio 0.51 (IQR 0.38–0.68), $P < .001$
$N = 5,539$ subjects	HOB elevation	SBT associated with:
To evaluate the impact of the ventilator bundle and its individual elements with the incidence of VAE, mechanical ventilation duration, hospital length of stay, and hospital mortality	Stress ulcer prophylaxis	Decreased time to extubation: hazard ratio 2.48 (IQR 2.23–2.76), $P < .001$
	SBT	Decreased risk for VAE: hazard ratio 0.55 (IQR 0.40–0.76), $P < .001$
		Decreased mortality risk: hazard ratio 0.28 (IQR 0.20–0.38), $P = .001$
		HOB elevation associated with:
		Decreased time to extubation: hazard ratio 1.38 (IQR 1.14–1.68), $P < .001$
		DVT prophylaxis associated with:
		Decreased time to extubation: hazard ratio 2.57 (IQR 1.80–3.66), $P < .001$
		Oral care with chlorhexidine associated with:
		Increased mortality risk during mechanical ventilation: hazard ratio 1.63 (IQR 1.15–2.31), $P = .006$
		Stress ulcer prophylaxis associated with:
		Increased VAP risk: hazard ratio 7.69 (IQR 1.44–41.10), $P = .02$

Table 3. Continued

Study/Design Setting and Objective(s)	Bundle Characteristics	Major Findings
O'Horo et al 2016 ⁹⁸	DSI	Oral care with chlorhexidine was the only bundle element associated with VAE: hazard ratio 0.44 (IQR 0.26–0.77)*
Retrospective, single-center, observational cohort study	DVT prophylaxis	Adherence with stress ulcer prophylaxis had a borderline association with increased VAE risk: hazard ratio 1.59 (IQR 1.00–2.50)*
All adult ICUs studied over 31 months	Oral care with chlorhexidine	
<i>N</i> = 2,660 subjects	Stress-ulcer prophylaxis	
To evaluate the incidence of VAE within 2 d of failure to meet any bundle element		
Harris et al 2018 ⁹⁹	HOB elevation 30–45°	No difference between bundle scores in VAE cases vs. controls 3 d prior to VAE onset: 0.73 and 0.70, respectively
Prospective, single-center observational case-control study (ratio of 1:4, respectively)	SBT: daily assessment	OR 1.15, <i>P</i> = .34
<i>n</i> = 273 cases <i>n</i> = 1,092 controls	Targeted sedation by RASS	No difference in oral care score between VAE cases and controls 3 days prior to VAE onset
To determine whether decreased adherence with the ventilator bundle increased VAE risk	Oral care with chlorhexidine	OR 1.13, <i>P</i> = .38
		Oral care with chlorhexidine: only variable associated with increased VAE risk for all subjects:
		At 3 d mechanical ventilation: OR 1.45, <i>P</i> = .007
		At ≥ 7 d mechanical ventilation: OR 1.42, <i>P</i> = .03
		With IVAC and PVAP: OR 1.73, <i>P</i> = .0006
		And in multivariate analysis: OR 1.45, <i>P</i> = .008

* Adjusted for APACHE III and gender.
 VAE = ventilator-associated event
 DSI = daily sedation interruption
 VAC = ventilator-associated condition
 IVAC = infection-related ventilator-associated condition
 VAP = ventilator-associated pneumonia
 HOB = head of bed
 SBT = spontaneous breathing trial
 SSD = subglottic secretion drainage
 OR = odds ratio
 IQR = interquartile range
 DVT = deep vein thrombosis
 RASS = Richmond Agitation-Sedation Scale

bundle components: head of bed elevation, oral care with chlorhexidine, DSI, and SBT.

Ding et al⁹⁴ found no difference in VAC or IVAC before or after bundle implementation, yet the overall incidence of VAE was low; the investigators noted that many of the bundle components already were practiced ad hoc (prior to formal implementation), but their use was poorly documented. Muscedere et al⁹⁵ found increased bundle adherence was associated with decreased VAC but not IVAC.⁹⁵ However, individual bundle components were not associated with VAC or IVAC in multivariate logistic regression modeling. Interestingly, the percentage of days when stipulated DSI or SBT were performed produced salient trends toward protection from VAC and IVAC. Nevertheless, interpreting these results is limited because of suboptimal bundle compliance. Lewis et al⁹⁶ reported that none of the 6 ventilator bundle components was associated with either VAC or IVAC.

In later studies (in 2016 and 2018),^{97–99} the only common practices were oral care with chlorhexidine and either

DSI or targeted light sedation (both are indistinguishable in their impact on duration of mechanical ventilation).¹⁰¹ These studies were substantially larger than the earlier studies (ie, cumulative sample size of 9,564 vs 2,224, respectively), and their results were more informative.

Klompas et al⁹⁷ reported that DSI, SBT, thrombosis prophylaxis, and semi-recumbent positioning were independently associated with reduced duration of mechanical ventilation. However, only SBT was associated with decreased VAE incidence despite under-performance (ie, 25–33% of ventilator days that required SBT). They also reported increased mortality risk associated with chlorhexidine, as well as increased VAP risk associated with stress ulcer prophylaxis.

O'Horo et al⁹⁸ found a salient trend between stress ulcer prophylaxis and VAE risk, and a significant reduction in VAE risk with chlorhexidine. However, interpreting their results is limited because of overall low VAE incidence. The most interesting (and only prospective) study examined VAE incidence within 2 d of failure to implement any

bundle element. Harris et al⁹⁹ scored both overall daily and cumulative compliance with the ventilator bundle. They reported no difference between ventilator bundle compliance and the development of VAE. However, oral care with chlorhexidine again was associated with increased VAE risk.

Pileggi et al¹⁰⁰ reported that ventilator bundle implementation was associated with reduced overall ICU mortality (odds ratio 0.90 [IQR 0.84–0.97]). Moreover, in a subset of studies reporting VAP-related mortality, the ventilator bundle was associated with a considerably larger reduction in mortality risk (odds ratio 0.71 [IQR 0.52–0.97]). Despite these promising results, bundle compliance varied widely (20–99.8%), and the studies themselves were of poor quality.

Barriers and Unresolved Issues

Common themes that emerged in the discussions of these studies are the impact of non-modifiable risk factors, the impact of individual bundle components on VAE, and uncertainty regarding how ventilator bundle adherence might impact VAE.

Because VAP and VAE are inter-related, non-modifiable risk factors for VAP also likely impact the incidence of VAE and thus ventilator bundle effectiveness. VAP risk is associated with numerous confounding variables such as poverty and homelessness (eg, malnutrition, ubiquitous dental disease), traumatic injuries, and immunosuppression,⁴ as well as previous exposure to antibiotic therapy.¹⁰²

Moreover, what constitutes modifiable versus non-modifiable factors remains unclear. For example, men are at increased risk for developing VAE.^{98,103} Boyer et al¹⁰⁴ found that only 37% of VAC instances were preventable, whereas 40% were attributable to non-infectious sources (eg, ARDS, pulmonary edema, atelectasis). Other risk factors, such as intra-abdominal hypertension and sepsis, are, at best, questionably modifiable. Intra-abdominal hypertension often develops after abdominal trauma, burns, and other conditions,^{8,105} and it is associated with VAP.¹⁰⁶ The incidence and associated mortality with severe sepsis is related to poverty,¹⁰⁵ poor access to medical care,¹⁰⁷ and race.¹⁰⁸ Therefore, preventing VAE in these subgroups is uncertain, if not unknown.

Another issue is that specific bundle elements, as well as other therapies vital to caring for the critically ill, appear to be at cross purposes with VAP or VAE reduction. Two studies found that stress ulcer prophylaxis was associated (or approached significant association) with increased VAP risk.^{95,97} In addition, enteral feeding increases VAP risk.^{109,110} Both therapies are crucial and therefore must be considered as non-modifiable risk factors for VAP and probably VAE as well.

The greatest concern raised in the reviewed studies (as well as others) is evidence that oral care with chlorhexidine increases both VAE risk⁹⁹ and mortality risk.^{97,111,112} Yet the pathophysiologic mechanism in intubated subjects remains unclear. ARDS following either gross aspiration or inadvertent intravenous administration of chlorhexidine have been documented,^{113,114} as has an animal model demonstrating acute lung injury following intra-tracheal administration.¹¹⁵ These reports are mechanistically consistent with an observational study in which mortality risk was restricted to non-intubated subjects.¹¹¹ Moreover, in addition to causing oral mucosa damage and, by extension, lung epithelial injury, chlorhexidine may promote bacterial resistance and accelerate acquired resistance.¹¹⁶ Because chlorhexidine's apparent effectiveness in reducing VAP is limited to unblinded studies,¹¹⁷ its continued inclusion in ventilator bundles should be reconsidered.

A particularly intriguing issue was determining the “dosage” or impact of missing bundle components and its window of effect on the incidence of VAE.⁹⁸ For example, we cannot determine the temporal threshold at which positioning of the head of bed below 25° translates into quantifiable and meaningful VAE risk. The same quandary applies to missing episodes of oral care, DSI, or SBT. There also is the problem of false conclusion bias, ie, that performing a particular bundle element necessarily implies a meaningful reduction in VAE risk. For example, performing an SBT will not impact VAE risk if a positive test does not expeditiously result in an extubation trial (in those without contraindications).

At this juncture, no high-level evidence supports the notion that current ventilator bundles reduce VAE risk. In addition, chlorhexidine and stress ulcer prophylaxis may promote VAE. Even if chlorhexidine prophylaxis is discontinued in the future, stress ulcer prophylaxis will continue regardless of VAE risk. In contrast, reducing mechanical ventilation duration (ie, via DSI, targeted light sedation, or SBT) should remain a central feature of any VAE-prevention bundle.

Moreover, the VAE paradigm presents the opportunity to fashion a more expansive bundle. In one of the reviewed studies, positive fluid balance tended to increase VAC risk (odds ratio 1.2 [IQR 1.0–1.4]).⁹⁶ Both hydrostatic and altered permeability pulmonary edema respond to neutral or negative fluid balance with improved oxygenation and reduced mechanical ventilation duration.^{52,118–120} Therefore, any new iteration of a ventilator bundle for VAE prophylaxis should include conservative fluid management guidelines.

Summary

Since 2013, only 6 predominantly retrospective studies have examined the utility of ventilator bundles to reduce

the incidence of VAE, while another examined its impact on mortality. The study findings were collectively inconsistent, and the quality of evidence was insufficient to drive public policy. They do, however, provide the basis for designing future, high-level, prospective studies to determine the potential value of specific bundle elements in reducing the incidence of VAE. At this juncture, and based on limited evidence, DSI and SBT appear to be the factors most likely to reduce VAE.

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