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Ventilator-associated Pneumonia Prevention
Is It Worth It?

Ventilator-associated pneumonia (VAP) continues to be a clinically important hospital-acquired infection. A recent prospective surveillance study found that VAP prevalence was 15.6% globally (13.5% in the United States, 19.4% in Europe, 13.8% in Latin America, and 16.0% in Asia Pacific), with a corresponding global *Pseudomonas aeruginosa* VAP prevalence of 4.1% (corresponding regional prevalence rates of 3.4, 4.8, 4.6, and 3.2%, respectively) (1). VAP is also associated with excess attributable mortality, although the magnitude of the mortality excess appears to be greatest for surgical patients and patients with midrange severity of illness (2). Hospital lengths of stay and medical care costs are also greater for critically ill patients who develop VAP (3). Most important, VAP is increasingly attributed to antibiotic-resistant bacteria including methicillin-resistant *Staphylococcus aureus*, nonfermenting gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia*), and antibiotic-resistant *Enterobacteriaceae* (extended-spectrum β-lactamase and carbapenem-resistant strains).

There has been a sense in the United States that VAP is a "vanishing" infection with reported mean national rates within intensive care units (ICUs) of less than 4 per 1,000 ventilator days (4). This is in contrast to higher rates of VAP reported internationally (1, 4). An important explanation for this discrepancy regarding nationally reported rates of VAP is the method of surveillance employed. The Centers for Disease Control and Prevention surveillance method markedly underestimates the occurrence of clinically and microbiologically confirmed VAP (5). This had led the Centers for Disease Control and Prevention and the National Health Safety Network to adopt ventilator-associated events as a new method of ICU surveillance, focusing on oxygenation parameters. Unfortunately, ventilator-associated events appear to underestimate the occurrence of VAP and often identify clinical events that are related to the underlying disease process and are not potentially preventable (6, 7). A deemphasis of the importance of VAP could motivate hospitals to reallocate funds and resources used for VAP surveillance and prevention to other clinical problems, especially if the latter are more closely tied to reimbursement. This could promote increasing future rates of VAP and greater overall healthcare costs.

In this issue of the *Journal*, Branch-Elliman and colleagues (pp. 57–63) performed a cost–benefit analysis using model inputs from the medical literature and the US Department of Labor to determine the preferred VAP prevention strategy, both from the hospital and societal perspectives (8). They attempted to identify the overall least expensive strategy and the strategy with the best cost–benefit ratio. The preferred strategies from the hospital perspective included the use of subglottic suction endotracheal tubes, probiotics, and the Institute for Healthcare Improvement VAP Prevention Bundle. The preferred strategies from the point of view of society also included oral care with chlorhexidine and selective oral decontamination. Several important limitations of this analysis should be noted. First, some of the assumptions on

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which this analysis was based are from clinical studies that are more than a decade old. The costs of medical care and the costs associated with infection acquisition have increased during this period, introducing a potential bias in this analysis. Second, the authors fail to take into account the costs associated with complications from the VAP prevention interventions. For example, selective oral decontamination can be associated with the emergence of antibiotic resistance, and probiotic administration could result in bacteremia. Third, this cost analysis did not examine bundles other than the Institute for Healthcare Improvement bundle that have been demonstrated to be potentially more robust in preventing VAP (9). Finally, the overall effect of increasing antibiotic resistance in VAP was not factored into this cost analysis. It is very likely that increasing rates of VAP attributed to antibiotic-resistant bacteria will result in greater ICU and hospital lengths of stay and greater costs (10). This change in the etiology of VAP could potentially make more expensive preventative measures cost-effective if they were able to reduce the occurrence of these antibiotic-resistant infections.

Other investigators have attempted to systematically review the evidence in support of VAP prevention strategies to identify the most clinically meaningful interventions to employ. Roquilly and colleagues performed a recent systematic review to determine which pneumonia prevention methods applied in the ICU are most effective for decreasing mortality rates and reducing mechanical ventilation duration (11). They evaluated all appropriate randomized controlled trials of digestive prophylactic methods (selective digestive decontamination, acidification of gastric contents, early enteral feeding, prevention of microaspiration), circuit prophylactic methods (closed suctioning systems, early tracheotomy, aerosolized antibiotics, humidification, lung secretion drainage, silver-coated endotracheal tubes), or oropharyngeal prophylactic methods (selective oral decontamination, patient position, sinusitis prophylaxis, subglottic secretion drainage, tracheal cuff monitoring). Only selective digestive decontamination significantly decreased mortality among all the interventions evaluated, whereas mechanical ventilation duration was reduced in trials evaluating selective digestive decontamination and physiotherapy. A major limitation of this analysis was that bundled therapy was not examined. Nevertheless, if one assumes that the most cost-effective therapy is the one with the greatest clinical efficacy, then selective digestive decontamination would be a preferred method by this analysis.

Selective digestive decontamination and the use of silver-coated endotracheal tubes were not found to be cost-effective interventions by Branch-Elliman and colleagues primarily because of the high costs associated with their application, despite their demonstrated clinical effectiveness (12, 13). However, the increasing prevalence of VAP attributed to multidrug-resistant organisms mandates that more effective preventative measures be evaluated even if they are potentially more expensive. Several examples of such interventions include the use of aerosolized antibiotics and immunotherapies. Palmer and colleagues showed that aerosolized antibiotics could effectively eradicate multidrug-resistant organisms from the respiratory tract of ventilated patients while also reducing the pressure from systemic antibiotic therapy to promote new colonization with resistant pathogens (14). Similarly, Que and colleagues studied panobacumab, a fully human antilipopolysaccharide monoclonal antibody targeting VAP resulting from *P. aeruginosa* (15). In this pilot study, panobacumab adjunctive immunotherapy was associated with improved clinical outcome in a shorter time. Both of these approaches could be used to target the prevention of VAP by multidrug-resistant organisms. However, given their expense, it is unlikely that these interventions would be considered cost-effective using the definitions applied by Branch-Elliman and colleagues, even if they are demonstrated to be clinically effective.

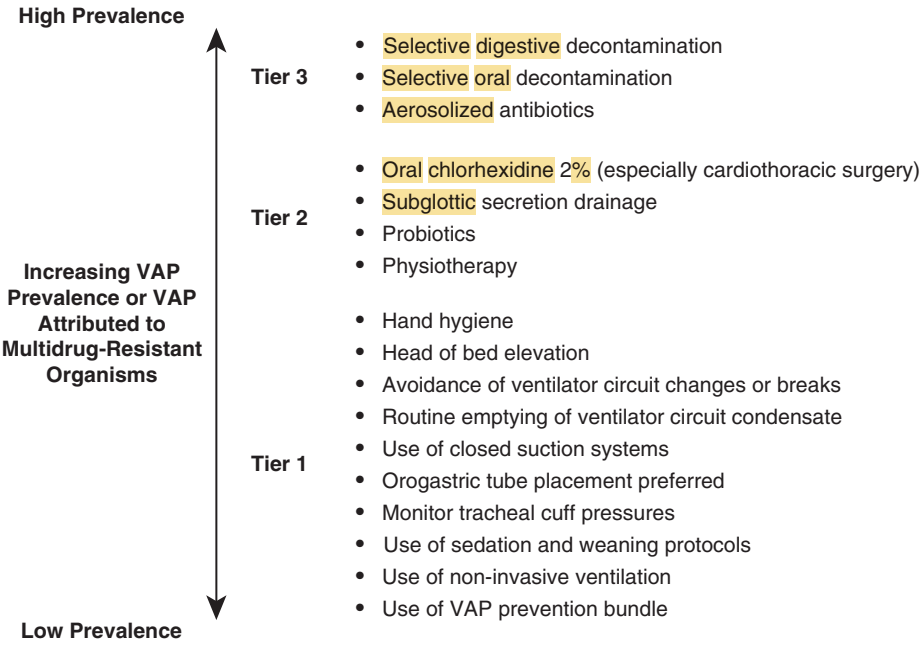

Figure 1. Tiered approach of preventative strategies for ventilator-associated pneumonia (VAP).

In summary, economic pressures mandate that the most cost-effective approaches for the prevention of VAP be applied. In healthcare settings in which VAP rates are high, especially VAP attributed to multidrug-resistant organisms, the use of more expensive preventative measures could be justified if they reduced overall costs and potentially improved outcomes. Figure 1 provides a tiered approach for the application of VAP prevention measures based on their perceived cost-effectiveness relative to the magnitude of the local problem with VAP. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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The Lungs and the Heart

Twenty-five years ago, J. Butler wrote a review article on cardiac dysfunction in obstructive lung disease entitled "The heart is not always in good hands" (1). The review was based primarily on two landmark studies from his group that were published in the *Journal* a few years before (2, 3). Butler and colleagues had shown that air trapping during tachypnea in patients with chronic obstructive pulmonary disease (COPD) causes a rise in left ventricular end-diastolic pressures, indicating a filling disturbance of the left ventricle during dynamic hyperinflation (3). Did we give sufficient attention to this physiologic concept when evaluating lung–heart interactions in patients with COPD during the last decades? To be honest, I do not think so. It was not until 10 years after Butler's review that Boussuges and colleagues reported in the *Journal* a decreased left atrial filling and a decreased left ventricular preload on echocardiography in patients with severe COPD (4). Furthermore, Funk and colleagues (5) showed that this left ventricular filling disturbance is also present in patients with COPD who have a normal pulmonary artery pressure. The clinical relevance of left ventricular filling dysfunction was demonstrated by me and my colleagues in a cohort of 170 patients with COPD in whom physical activity and 6-minute-walk distance were reduced when there was an impaired left ventricular diastolic filling pattern (6, 7). Finally, several interventional studies showed that deflation of the lung by lung volume reduction surgery is associated with improved left ventricular filling on echocardiography (8), a decrease in wedge pressure (9), and an improved oxygen pulse during exercise (10). Last but not least, Barr and colleagues (11) observed an inverse relationship between increasing airway obstruction and increasing emphysema by high-resolution computed tomography and decreasing left ventricular volume during cardiac magnetic resonance imaging in healthy subjects (11). A similar relationship between increasing static lung hyperinflation and decreasing left ventricular diameter on echocardiography was found in patients with COPD (7).

ORIGINAL ARTICLE

Determining the Ideal Strategy for Ventilator-associated Pneumonia Prevention

Cost–Benefit Analysis

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Abstract

Rationale: Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection with high associated cost and poor patient outcomes. Many strategies for VAP reduction have been evaluated. However, the combination of strategies with the optimal cost–benefit ratio remains unknown.

Objectives: To determine the preferred VAP prevention strategy, both from the hospital and societal perspectives.

Methods: A cost–benefit decision model with a Markov model was constructed. Baseline probability of VAP, death, reintubation, and discharge from the intensive care unit (ICU) alive were ascertained from clinical trial data. Model inputs were obtained from the medical literature and the U.S. Department of Labor; a device cost was obtained from the manufacturer. Sensitivity analyses were completed to test the robustness of model results.

Measurements and Main Results: Overall least expensive strategy and the strategy with the best cost–benefit ratio, up to a willingness to pay threshold of $50,000–100,000 per case of VAP averted was sought. We examined a total of 120 unique combinations of VAP prevention strategies. The preferred strategy from the hospital perspective included subglottic suction endotracheal tubes, probiotics, and the Institute for Healthcare Improvement VAP Prevention Bundle. The preferred strategy from the point of view of society also included additional prevention measures (oral care with chlorhexidine and selective oral decontamination). No preferred strategies included silver endotracheal tubes or selective gut decontamination.

Conclusions: Despite their infrequent use, current data suggest that the use of prophylactic probiotics and subglottic endotracheal tubes are cost-effective for preventing VAP from the societal and hospital perspectives.

Keywords: ventilator-associated pneumonia; prevention; healthcare-associated infection; cost–benefit analysis

Ventilator-associated pneumonia (VAP) is a preventable healthcare-associated infection with mortality rates that may exceed 10%. Although VAP definitions are controversial, and many hospitals report rates close to zero, 5–15% of ventilated patients continue to suffer from healthcare-associated pneumonia (1, 2). VAP is estimated to cost between $10,000 (3) and $60,000, in 2013 U.S. dollars (3–5).

Many strategies to prevent VAP have been evaluated in clinical trials; strategies with demonstrated efficacy include the Institute for Healthcare Improvement (IHI) VAP prevention bundle (IHI bundle) (6), oral care with and without chlorhexidine (7, 8), subglottic suction endotracheal tubes (9–11), silver-coated endotracheal tubes (12), probiotics (13, 14), and both selective oral and selective gut decontamination (15). However, with

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At a Glance Commentary

Scientific Knowledge on the Subject: Although many clinical trials have focused on prevention of ventilator-associated pneumonia (VAP), no prior studies have compared multiple different prevention strategies head-to-head, or multiple different strategies in combination.

What This Study Adds to the Field: Here we present the results of a cost–benefit analysis, designed to determine the most cost-effective elements of a VAP prevention program. In line with recommendations from the *Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals*, the decision model found that suction endotracheal tubes are a cost-effective VAP prevention strategy under all conditions studied. The use of probiotics is another prevention strategy that may be preferred in most clinical settings.

the exception of the IHI bundle and oral care (16), little is known about the comparative effectiveness of these different strategies, or their effectiveness when used in combination.

Developing an appropriate, cost-effective VAP prevention program is an important problem facing both individual hospitals and society. Although the National Healthcare Safety Network definitions have recently shifted to focus on ventilator-associated conditions and possible or probable VAP (17), national recommendations for prevention still focus on VAP and VAP prevention trials (18). Understanding which combination of strategies is most cost-effective for VAP prevention requires careful consideration of all effective prevention strategies, considering the relative cost and effectiveness of each (19).

Despite multiple clinical trials and guidance from specialty societies, little is known about which strategies have the best cost–benefit ratio from the point of view of society and the hospital. To this end, we sought to develop a comparative effectiveness model to determine the most cost-effective VAP prevention package from the points of view of the hospital and of society. Partial study results have been previously reported in the form of an abstract (20).

Methods

Model Construction

We created a decision tree with a Markov model simulating patient-days in the intensive care unit (ICU) (Figure 1). The decision tree included all possible combinations of prevention strategies (Figure 2). The Markov model included all possible states within the ICU setting, and simulated a 28-day period with a theoretical cohort of 10,000,000 patients.

Model Inputs

Baseline primary data for daily risk of intubation, extubation, VAP, and death over a 28-day period were obtained from a previously published multicenter prospective study examining outcomes for patients receiving mechanical ventilation. At the time, VAP prevention practice was not standard (21), allowing us to estimate baseline rates without preventive interventions. The probability of key variables (death, VAP, extubation, reintubation, and ICU survival) on a daily basis was obtained directly from Esteban and coworkers (21). The total incidence of VAP was 9.8%, and risk varied depending on the duration of intubation (e.g., 8% on Day 1 and 18% on Day 7).

The effectiveness of each prevention strategy was obtained from the literature (Table 1). We evaluated 120 unique prevention combinations, including three types of endotracheal tube (standard, silver, suction) and five different prevention strategies (IHI bundle with and without chlorhexidine oral care, probiotics, selective oral decontamination, and selective gut decontamination). Different types of endotracheal tubes were treated as competitive alternatives that could not be used together. If clinical trial data regarding combinations of VAP prevention strategies were available, such as in the case of the IHI bundle and oral care, then these data were used. In cases where data regarding the use of multiple strategies in combination were unavailable, we assumed that strategies used in combination maintained their mean risk reduction effectiveness.

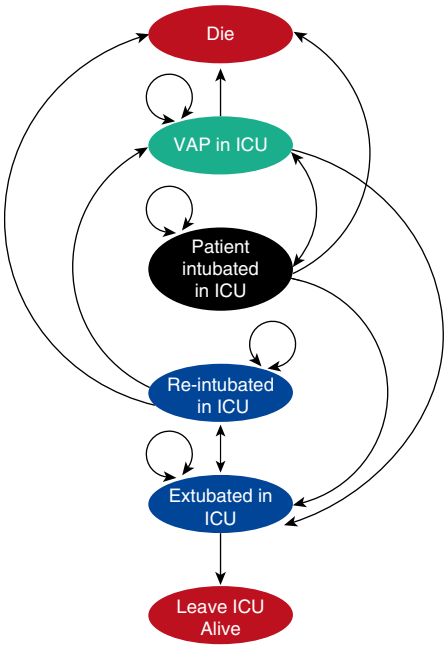

Figure 1. Schematic of Markov model, showing all possible states for intubated patients in the ICU. All patients start in the same state, that is, intubated in the ICU, represented by the *black oval*. The *green oval* highlights the VAP state, and the *blue ovals* represent transitional states. *Red ovals* indicate "terminal" Markov states, meaning that once in one of these categories, theoretical patients exit the model. ICU = intensive care unit; VAP = ventilator-associated pneumonia.

Estimates of cost were obtained from the literature, from the U.S. Department of Labor Statistics (median nursing wages) (22), the Pharmacy Red Book (23), or directly from the manufacturer if not otherwise available (personal communication, silver-coated endotracheal tubes only). Most costs were included on a daily recurrent basis. Recurrent costs were included as the sum of the total cost of each of the prevention strategies multiplied by the number of days spent intubated in the ICU. Endotracheal tubes were treated as a one-time cost unless the patient was reintubated, in which case a second endotracheal tube cost was included (Table 1). Daily estimates of nursing time required for prevention were based on our previously published work (24).

Preferred Prevention Strategies

The primary outcome was the strategy with the best cost–benefit ratio (hospital-preferred strategy, or the overall least expensive strategy). Our secondary outcome was the strategy with the highest benefits

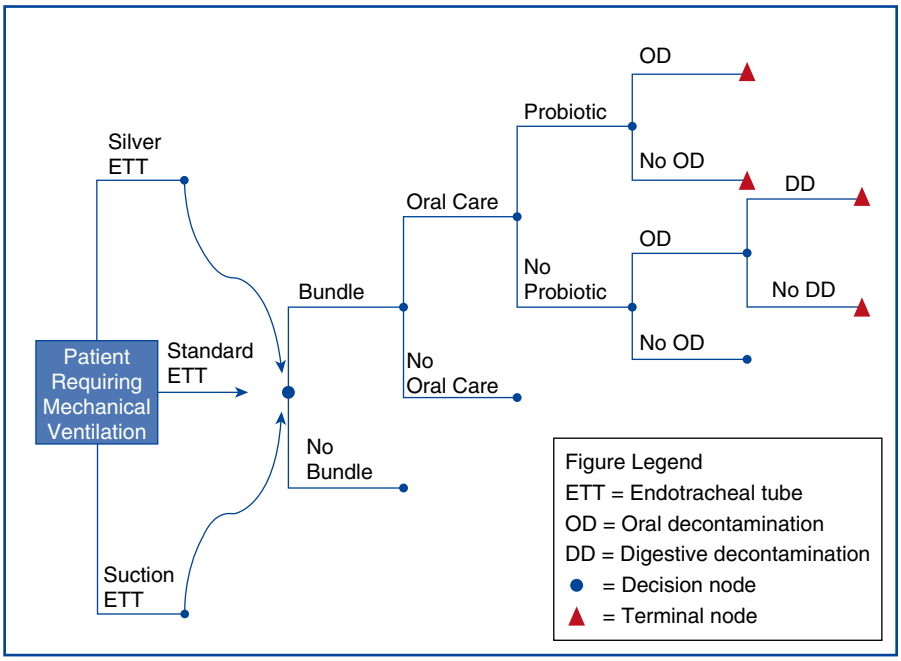

Figure 2. Schematic of the decision model. *Circles* indicate decision nodes, in which additional ventilator-associated pneumonia prevention options may be chosen. *Triangles* indicate terminal nodes, which indicate that no additional options are available. Three prevention options are mutually exclusive (silver endotracheal tube, subglottic suction endotracheal tube, and standard endotracheal tube), and other prevention options are competing choice (meaning that none, any, or all have the potential to be included in the most cost-beneficial model).

with a maximum willingness to pay threshold of $50,000–100,000 per case of VAP averted (society-preferred strategy).

Sensitivity Analysis

One-way sensitivity analysis. To test the robustness of model output, one-way sensitivity analyses and threshold analyses were run on all estimates. For variables with 95% confidence intervals available from the literature, the confidence interval was used. If multiple studies addressed the same question (as in the case of probiotics), then the highest possible and the lowest possible estimates from all published trials were chosen. If no clear literature estimate was available, then the clinicians involved in the study determined a range of plausible estimates and used the plausible range in the model to determine if different estimates changed results. The range of values evaluated is shown in Table 1. For two-way sensitivity analysis methods, see the online supplement.

Model Validation

To ensure that our baseline Markov model accurately represented patient time in the ICU, we ran a base-case simulation of 28 days. We then compared the model output with detailed results from a published cohort study of ICU outcomes (21) to determine the overall robustness of the base-case scenario (Figure 3).

Results

We evaluated 120 unique prevention combinations, simulating probability of developing VAP over a month-long period in the ICU. Detailed outcomes for selected strategies are included in the online supplement.

Preferred Prevention Strategies

The strategy with the best cost–benefit ratio (the preferred strategy from the hospital perspective) included a suction endotracheal tube, the IHI bundle without oral care, and probiotics (Figure 4). The preferred strategy from the societal perspective, assuming a willingness-to-pay threshold per case of VAP prevented of $50,000, included a suction endotracheal tube, probiotics, the IHI bundle including oral care, and selective oral decontamination. Selective gut decontamination was not a preferred strategy

Table 1. Prevention Strategies Included in Model, with Cost, Relative Risk Reduction, Range of Risk Reduction Values Tested, and Type of Cost

Strategies and Costs	Cost		RR		Cost Type
	Median Estimate	Range	Median Estimate	Range	
Standard ETT	$3.07	$0–10	1	n/a	Fixed
Silver ETT	$50	$30–60	0.61	0.5–1.0	Fixed
Suction ETT	$17.16	$10–100	0.51		Fixed
VAP bundle	$33.32	$33.32–150	0.29	0.1–0.8	Recurrent
Oral care	$38.00	$38–150	0.67	0.5–0.75	Recurrent
VAP bundle and oral care	$71.32	$71–300	0.11	0.05–0.5	Recurrent
Probiotics	$2.18	$1–10	0.48	0.1–0.9	Recurrent
Oral decontamination	$13.30	$5–25.00	0.69	0.2–0.8	Recurrent
Digestive decontamination	$17.92	$9.00–45.00	0.47	0.2–0.8	Recurrent
Cost of VAP	$15,957.90	$7,000–35,000	—	n/a	Fixed
Nursing time cost*	$33.32	$25.00–120.00	—	n/a	Recurrent

Definition of abbreviations: ETT = endotracheal tube; n/a = not applicable; RR = risk reduction; VAP = ventilator-associated pneumonia.
*Per hour.

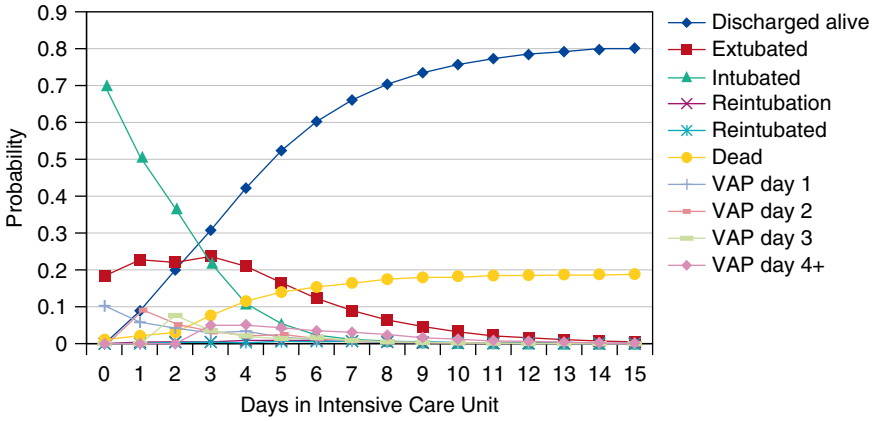

Figure 3. Results of the base-case analysis of patients in the intensive care unit. Several different clinical states are included. After 15 days, approximately 80% of the patients were discharged from the intensive care unit alive, and approximately 18% died. The remaining patients were either intubated or had VAP. Note that because discharge alive and death are both terminal states, these probabilities are cumulative probabilities, whereas the other states represent snapshots of the daily probability of being in that clinical state. "Reintubation" represents the day reintubation occurred, and "reintubated" represents a later day after the reintubation. VAP = ventilator-associated pneumonia.

for the hospital or society up to willingness to pay per case of VAP prevented up to $100,000. All strategies including the use of a silver-coated endotracheal tube were dominated by suction endotracheal tubes, because of the higher cost and lower efficacy of the silver-coated tubes compared with suction endotracheal tubes.

One-Way Sensitivity Analysis

Even through a wide range of values (Table 1), varying estimates did not significantly alter the preferred strategies from the viewpoint of the hospital or society, with the exception of nursing wages in the case of the IHI bundle. Within a reasonable range of cost estimates for both standard endotracheal tubes and subglottic suction endotracheal tubes, the preferred strategy remained unchanged; subglottic suction endotracheal tubes were included in all circumstances.

Critical inputs that would change the preferred strategy from the hospital perspective included hourly nursing wage, effectiveness of probiotics, effectiveness of the IHI bundle, and oral care in combination. Costs that changed preferred strategy included medication costs (selective oral decontamination), cost of the oral care kit, and nursing time costs. Of note, altering the risk reduction associated with selective gut decontamination in favor of improving the effectiveness of this strategy did not result in inclusion of this prevention strategy.

We used U.S. Department of Labor Statistics data for our base estimate of nursing hourly wage ($33.32) (22); the choice of optimal model changes considerably when the hourly wage of the ICU nurse increases to more than $67. At this level, the IHI bundle becomes cost-ineffective, because this strategy is nursing-time intensive, and the cost–benefit of this strategy changes with increasing nursing wages. Although $67 per hour is substantially higher than the national median nursing wage, it is within the range of ICU nursing wages at some facilities, and so would change the preferred strategy in some institutions. Given interinstitutional variability in nursing wages, the IHI bundle may be cost-effective at some hospitals but not at others.

The use of probiotics for VAP prevention was used in nearly every scenario because of the low cost of the strategy. However, as the risk reduction associated with probiotics was increased in sensitivity analyses, the preferred strategy from the perspective of society used fewer additional prevention techniques, as the cost-to-absolute benefit of these strategies increased substantially.

The cost of medications for selective oral decontamination and the cost of the oral care kit both affected the preferred strategy from the societal point of view. At low cost estimates for oral decontamination, oral decontamination is included instead of standard oral care. Similarly, at low cost estimates for the oral care kit, the oral care strategy is chosen over oral decontamination. In mid-range cost estimates for both of these two variables, the optimal strategy becomes dependent on willingness to pay per case of VAP prevented. In the high range of price estimates for each, only one of these two strategies is included.

Varying the cost estimate of VAP also changed the optimal strategy from the point of view of society; at low cost estimates of VAP (range, $7,000–14,000), the preferred strategy from the societal perspective included a suction endotracheal tube, probiotics, and the IHI bundle. As the cost estimate of VAP increased, adding selective oral decontamination was cost-effective from society's, but not the hospital's, point of view.

Results for two-way sensitivity analysis are available in the online supplement.

Model Validation

Based on published ICU outcomes data, our base-case results were consistent with ventilated patient-time and outcomes in the ICU (Figure 3). Overall, 83.8% of patients left the ICU alive, 20% developed VAP, and 15.4% died. At the end of a 15-day period, 1% remained in the ICU.

Discussion

Our findings about the most cost-effective strategies for prevention of VAP provide support for many aspects of the recently published 2014 *Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals*, which was endorsed by more than 15 professional societies (18). Specifically, the *Compendium* recommends as basic practices the use of a subglottic endotracheal tube if mechanical ventilation is expected to last greater than or equal to 72 hours, key elements of the IHI bundle (semirecumbent positioning, a daily assessment of readiness to wean, and daily spontaneous breathing trials), and early mobility (18). Basic practices are those that should generally be applied to all ventilated patients (18).

The most important and potentially the most controversial change in the *Compendium* is the inclusion of subglottic suction endotracheal tubes as a basic practice. Our analysis supports this recommendation. From a cost–benefit perspective, subglottic suction endotracheal tubes are present in all preferred strategies

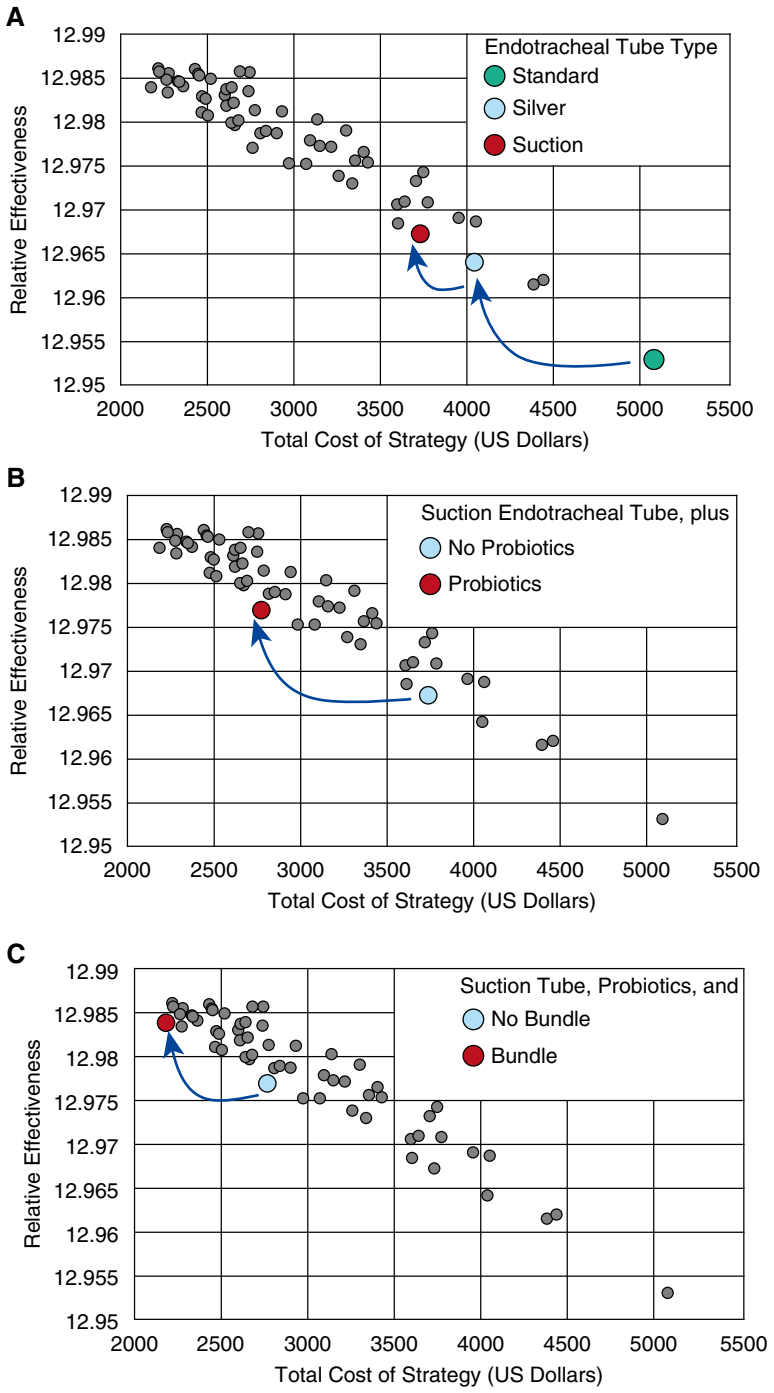

Figure 4. Isolated effect of key strategies on the relative cost–benefit of different ventilator-associated pneumonia prevention options. (*A*) Isolated effect of different types of endotracheal tube type. (*B*) Effect of adding probiotics to suction endotracheal tubes. (*C*) Effect of adding the Institute for Healthcare Improvement bundle to suction endotracheal tubes and probiotics. Nonpreferred and unhighlighted strategies are presented in *gray* throughout.

from both the hospital and societal perspectives, even among patients intubated for only 1–2 days. The suction endotracheal tubes were also cost-effective across a broad range of tube cost estimates, as high as $100 per tube, suggesting that even in the event of high infrastructure and personnel costs, this strategy is overall cost-saving. We included extremely high cost estimates in the case of subglottic suction endotracheal tubes in part to reflect hypothetical but potentially severe consequences of this strategy, including the theoretical risk of tracheal mucosal injury (25, 26). The IHI bundle was included in preferred strategies from both the hospital and societal perspectives, in agreement with *Compendium* recommendations.

As "special approaches" to be used when VAP rates remain high in spite of basic practices, the *Compendium* included probiotics, oral care with chlorhexidine, and selective oral/digestive decontamination, among other interventions (18). Interestingly, in our analysis, probiotics were included in all preferred VAP prevention strategies, primarily because of their overall low cost (<$2 per day) and ease of administration (<5 minutes of nursing time per day). Despite the apparent attractiveness of using probiotics for VAP prevention, this strategy was included as a "special approach" rather than basic practice in the most recent *Compendium*. This designation likely resulted from the controversial clinical efficacy of prophylactic probiotics, with some studies demonstrating reductions in VAP rates as high as 50%, and others demonstrating no effect (27–29). However, we found that including probiotics is cost-effective, and included in the preferred strategy both from the hospital and the societal perspective, even when the reduction in rates of VAP associated with their use is as low as 2%.

Another concern with broad use of prophylactic probiotics is bloodstream infections, which occur but have rarely been reported (30). Our cost estimates did not include the additional costs of managing a bloodstream infection, but also did not consider other potential benefits of probiotics, including reduced incidence of *Clostridium difficile* infection (31); one randomized controlled trial of probiotics reported a 13% reduction in *C. difficile* infection (13). Because *C. difficile* infection is more common than probiotic-associated bacteremia, in total our model may have been biased against probiotics as a cost-effective prevention strategy. Despite this, probiotics were chosen as optimal under all conditions tested. An additional barrier to implementing probiotics for reduction of healthcare-associated infections may be regulatory; probiotics are not treated as a drug by the Federal Drug Administration, and thus may be difficult to administer to inpatients.

Another important change in the *Compendium* is the downgrading of

chlorhexidine oral care to a special practice. Our cost–benefit model found that oral care with chlorhexidine is an expensive option that exceeds usual cost-to-effectiveness parameters in most healthcare settings; this finding is consistent with the *Compendium* recommendation (18).

Finally, the *Compendium* included silver-coated endotracheal tubes in the category of "generally not recommended" (18). Our analysis supports this from a cost–benefit perspective: silver-coated endotracheal tubes were not present in any preferred strategy that we evaluated. We also found that selective digestive decontamination (15) was not a preferred strategy for VAP prevention from a cost–benefit perspective, primarily because of the high cost and nursing time required to implement this approach. The model also did not include negative consequences of pursuing this prevention strategy, including increased antimicrobial resistance and increased rates of *C. difficile* infection (32); adding these outcomes into the model would only worsen the attractiveness of this option.

When developing prevention policy, consideration must be given to the incidence and cost of the illness and the costs of implementing and executing prevention (19). Many infection control programs are cost-saving (33); however, overuse of prevention services can divert key patient care providers from other important patient-care activities (24). In general, strategies that cost between $50,000 and $100,000 per quality-adjusted life-year saved are considered to be "cost effective" in the United States (34, 35). For the purposes of our analysis, we considered the preferred strategy from both the perspective of the hospital (the least expensive overall strategy, taking into account both the cost of prevention and the cost of disease) and of society (with a willingness to pay per case averted of $50,000–100,000). Previous studies examining quality of life with VAP have assigned the state a utility of 0.88 when compared with usual, healthy living, which is typically assigned a utility of 1.0 (36). Even assuming that VAP lasts a full week, the overall reduction in quality-adjusted life-years is less than 1% over a year. Adjusting for this minor reduction in quality-adjusted life-years, a more reasonable cost effectiveness threshold per case of VAP averted might be $500–1,000. Under these stricter cost parameters, only three strategies (IHI bundle, suction endotracheal tubes, and probiotics) would be included in preferred prevention strategies, regardless of perspective.

In our cost–benefit analysis, the preferred prevention package was dependent on the baseline rate of VAP; in healthcare settings where VAP rates are high, spending additional time and prevention resources on VAP will reduce overall cost and potentially improve outcomes. In settings where VAP rates are low, however, healthcare quality resources might be more appropriately spent targeting other conditions.

Study Limitations

The principal limitation in our study is the same as any study of VAP: defining VAP itself (37). Studies may have used different definitions of infection, and that this may influence results. Nonetheless, our approach represents a synthesis of the best available data and provides important new information for policy makers and ICU providers seeking to implement prevention strategies. Our analysis did not include some potential costs of suction endotracheal tubes, such as new wall suction setups or staff training, which could significantly affect the total cost of implementing this strategy. However, because the actual costs are unknown, we were not able to assess them. Overall, using a suction endotracheal tube is cost-effective even with cost estimates of $100 per-tube, suggesting that they would still be included in a preferred strategy, even accounting for additional infrastructure costs. Our estimates of cost are based on current pharmacy costs and nursing wages. If these change significantly, the optimal strategy could change.

The baseline data used to develop and validate the model were published in 2002, and many weaning and sedation practices have changed since then. These changes may reduce VAP incidence. However, these data were used in part because the multicenter trial was conducted without VAP prevention strategies in place, and so could be used to define baseline probabilities in the absence of intervention. If the true incidence of VAP is lower, then the most cost-effective bundle would include fewer prevention options. Another limitation is that a second dataset was not available for model validation. However, outcomes in our base-case simulation are similar to rates reported in recent ICU clinical outcomes trials (38), which provides reassurance that our model is a reasonable reflection of real-world events.

In the design of our cost–benefit model, we assumed that all strategies maintained their median efficacy when used in combination. However, it is possible that there are diminishing returns to additional prevention. We addressed this limitation through our sensitivity analyses, in which we varied the effectiveness of each prevention strategy within a wide range of possible parameters. If two strategies were only partially additive, then the VAP reduction obtained would be less, and the combination would be less cost-effective than reported. However, we were unable to assess if any two strategies were antagonistic. For example, it is conceptually possible that selective digestive decontamination renders probiotics entirely ineffective. We were not able to explore this possibility more fully, because no clinical trial data are available to suggest how these two strategies might interact with one another.

Conclusions

Overall, our model supported most of the recommended basic practices suggested in the *Compendium* for preventing VAP. The major discrepancy between the model output and the recommendations is the use of probiotics; our model suggested that they are cost-effective, whereas the *Compendium* recommendations included them only under special circumstances. Subglottic suction endotracheal tubes were an attractive prevention strategy, despite their infrequent use. In the absence of clinical trial data examining the relative effectiveness of different combinations of VAP prevention strategies, this comparative effectiveness analysis provides a meaningful estimate of the relative cost–benefit of different bundled options. Implementation of these prevention strategies has the potential to improve patient outcomes and reduce health care costs. ■

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