Silver-Coated Endotracheal Tubes and Incidence of Ventilator-Associated Pneumonia
The NASCENT Randomized Trial

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Context Ventilator-associated pneumonia (VAP) causes substantial morbidity. A silver-coated endotracheal tube has been designed to reduce VAP incidence by preventing bacterial colonization and biofilm formation.

Objective To determine whether a silver-coated endotracheal tube would reduce the incidence of microbiologically confirmed VAP.

Design, Setting, and Participants Prospective, randomized, single-blind, controlled study conducted in 54 centers in North America. A total of 9417 adult patients (≥18 years) were screened between 2002 and 2006. A total of 2003 patients expected to require mechanical ventilation for 24 hours or longer were randomized.

Intervention Patients were assigned to undergo intubation with 1 of 2 high-volume, low-pressure endotracheal tubes, similar except for a silver coating on the experimental tube.

Main Outcome Measures Primary outcome was VAP incidence based on quantitative bronchoalveolar lavage fluid culture with 10⁴ colony-forming units/mL or greater in patients intubated for 24 hours or longer. Other outcomes were VAP incidence in all intubated patients, time to VAP onset, length of intubation and duration of intensive care unit and hospital stay, mortality, and adverse events.

Results Among patients intubated for 24 hours or longer, rates of microbiologically confirmed VAP were 4.8% (37/766 patients; 95% confidence interval [CI], 3.4%-6.6%) in the group receiving the silver-coated tube and 7.5% (56/743; 95% CI, 5.7%-9.7%) (P=.03) in the group receiving the uncoated tube (all intubated patients, 3.8% [37/968; 95% CI, 2.7%-5.2%] and 5.8% [56/964; 95% CI, 4.4%-7.5%] (P=.04)), with a relative risk reduction of 35.9% (95% CI, 1.2%-67.9%). The silver-coated endotracheal tube was associated with delayed occurrence of VAP (P= .005). No statistically significant between-group differences were observed in durations of intubation, intensive care unit stay, and hospital stay; mortality; and frequency and severity of adverse events.

Conclusion Patients receiving a silver-coated endotracheal tube had a statistically significant reduction in the incidence of VAP and delayed time to VAP occurrence compared with those receiving a similar, uncoated tube.

Trial Registration clinicaltrials.gov Identifier: NCT00148642

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VAP rates, but no single strategy completely eliminates VAP. Adherence to prevention guidelines is variable due to costs and lack of education, resources, and leadership. Furthermore, benefits are user-dependent and may subside if educational initiatives are not continually reinforced or monitored.

Coating the endotracheal tube with silver is theoretically attractive because silver has broad-spectrum antimicrobial activity in vitro, reduces bacterial adhesion to devices in vitro, and blocks biofilm formation on the device in animal models. A silver-coated tube has been developed with silver ions microdispersed in a proprietary polymer on both the inner and outer lumen, permitting ion migration to the tube surface to provide a sustained antimicrobial effect. The polymer may add to the antimicrobial activity of silver by blocking bacterial adhesion to the endotracheal tube. Silver is generally considered nontoxic; topical use to prevent infection after burns and other injuries is rarely associated with toxicity, based on extensive clinical experience. In a dog model, the silver-coated tube delayed colonization on the inner tube surface, decreased severity of lung colonization, and reduced histopathologically defined pneumonia. In a small randomized human study, the silver-coated tube was demonstrated to be clinically safe and to reduce the burden of bacterial airway colonization.

To determine if the silver-coated endotracheal tube would reduce the incidence of microbiologically confirmed VAP, we conducted the North American Silver-Coated Endotracheal Tube (NASCENT) Study, a prospective, randomized, multicenter, single-blind, controlled study in patients requiring mechanical ventilation for 24 hours or longer.

METHODS

Adults at least 18 years old were eligible for enrollment if they were expected to require mechanical ventilation with an endotracheal tube for 24 hours or longer. Exclusion criteria were participation in another study that conflicted with the current study, bronchiectasis, severe or massive hemoptysis, cystic fibrosis, pregnancy, silver sensitivity, and endotracheal intubation for longer than 12 hours within the preceding 30 days. Patients were recruited from December 2002 to March 2006 at 54 centers in North America. Each center’s institutional review board approved the study. Written informed consent was obtained from patients or their legally authorized representatives.

Patients were assigned in a 1:1 ratio to treatment groups according to a validated software-generated list created by FGK Clinical Research GmbH (Munich, Germany) using block randomization by site, with a fixed block length of 4. Each site received a series of sequentially numbered envelopes, each containing a randomization card for a study participant. Investigators were blinded to block length; microbiology laboratory personnel were blinded to group assignments.

Patients were to be intubated with large-cuff/long-length (high-volume/low-pressure) endotracheal tubes with a Hooded Murphy tip with eye, full McGill curve, tip-to-tip radiopaque line, and pilot balloon with self-sealing valve (internal diameter sizes, 7 to 9 mm). The experimental tube (Agento I.C.; C.R. Bard Inc, Covington, Georgia) and the control tube (Hi-Lo Endotracheal Tube; Mallinkrodt, St Louis, Missouri) were similar except for a silver coating on the experimental tube.

The protocol specified collection of patient data including daily monitoring of chest radiographs, clinical signs of VAP, adverse events, length of stay in the intensive care unit (ICU) and hospital, and mortality. Additional information collected in the case report form at study entry included demographic data, medical history, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and immunocompetency status. Additional information collected during the study included antibiotics used at the time of bronchoalveolar lavage (BAL) and methods of feeding, tracheal suctioning, and oral care. Sites were allowed to follow institutional practices for preventing VAP and were encouraged to avoid changing practices during the study.

Quantitative culture of BAL fluid was obtained if VAP was suspected or if new radiographic infiltrate plus qualifying clinical signs were present. Qualifying clinical signs were 2 of the following: fever or hypothermia, leukocytosis or leukopenia, or purulent tracheal aspirate (additional information available at http://pulmonary.wustl.edu/faculty/kollef.html). The primary outcome was VAP incidence based on quantitative BAL fluid culture with 10^4 colony-forming units/mL or greater in patients intubated for 24 hours or longer. Distal airway samples were obtained by directed bronchoscopy or nonbronchoscopic protected catheter (Combicath; KOL Biomedical, Chantilly, Virginia) (additional information available at http://pulmonary.wustl.edu/faculty/kollef.html).

Secondary outcomes were time to occurrence of VAP; durations of endotracheal intubation, ICU stay, and hospital stay; and mortality. In addition to these protocol-defined outcomes, we performed post hoc analyses of the incidence of VAP within 10 days of intubation and of the effect of VAP on secondary outcomes.

An independent data and safety monitoring board met before the study, supervised the investigation, and reviewed interim data after enrolling the first 20 patients and then after every 150 evaluable patients. The board was blinded to treatment group and had no formal or financial relationship to the sponsor other than compensation for consultations and related expenses. The board had access to all data and determined whether the study would be continued, terminated, or modified based on logistical issues relevant to study conduct, baseline data, outcomes, and safety. In addition, the board reviewed study progress, adherence to protocol, data quality, and other logistical issues. None of the interim analyses resulted in study termination based on predefined stopping rules.
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Statistical Analysis
Automated Planning and Evaluation of Sequential Trials software\(^2^{,29,30}\) was used to estimate sample size (additional information available at http://pulmonary.wustl.edu/faculty/kollef.html). Assuming a 15% incidence of VAP and 20% dropout in the first 24 hours, we calculated that approximately 1788 patients should be enrolled for a statistical power of 90% to detect a 30% reduction in the incidence of VAP, with a 2-sided significance level of .05. Analysis populations were defined prospecively (Figure 1). In modified intention-to-treat analyses, patients intubated for 24 hours or longer were analyzed as the primary efficacy population, and all intubated patients were analyzed for efficacy and safety.

Descriptive statistics were reported, and appropriate tests were used for baseline characteristics. Depending on the data distribution, the \(t\) or Mann-Whitney test was used to compare between-group differences in continuous variables. A \(\chi^2\) test was used for categorical variables. The primary outcome, VAP incidence, was analyzed by univariate technique using Planning and Evaluation of Sequential Trials software version 4.4 (University of Reading, Reading, England) for group sequential design to calculate triangular boundaries for binominal data (triangular test; additional information available at http://pulmonary.wustl.edu/faculty/kollef.html\(^2^{,30}\); all other analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

Multivariate regression analyses with a stepwise model selection procedure were performed to evaluate the influence of treatment group, as well as a list of predefined covariables, on VAP incidence (logistic regression\(^31\) and time to VAP onset (Cox regression). Predefined covariables were antibiotic therapy at intubation, APACHE II score, enteral nutrition, sex, total duration of intubation, hospital duration before study, oral care, continuous sedation, coma, chronic obstructive pulmonary disease, emergency surgery or trauma, and age. Variables with \(P > .10\) were eliminated from the final model. For secondary outcomes, a 2-sample \(t\) or Wilcoxon Mann-Whitney test was used for continuous variables, and a \(\chi^2\) test was used for categorical variables.

To control for multiplicity in analyses of primary and secondary outcomes, we combined Hochberg\(^32\) and closed hierarchical testing procedures. Kaplan-Meier analyses were performed using product-limit survival estimates with the generalized Wilcoxon test for statistical comparisons. All \(P\) values were 2-sided; significance was set at \(P < .05\).

RESULTS
A total of 9417 patients were screened (Figure 1); 7414 were not enrolled because they were not able to provide informed consent or were unlikely to require intubation for 24 hours or longer. Of 2003 randomized patients, 71 were never intubated and thus were excluded from the modified intention-to-treat analyses. Of the remaining 1932 patients, 423 were intubated for less than 24 hours.

Patients were evenly distributed between groups based on demographic and other baseline characteristics, including patients who were intubated for 24 hours or longer (n = 1509) and all intubated patients (n = 1932) (Table 1), except for history of chronic obstructive pulmonary disease (silver-coated vs uncoated, 11.6% vs 16.4% [\(P = .007\); all intubated patients, 9.2% vs 12.7% [\(P = .02\)]. No differences were noted between groups in APACHE II scores, use of enteral nutrition, presence of immunodeficiency, or other risk factors for VAP (additional information available at http://pulmonary.wustl.edu/faculty/kollef.html). No between-group differences were noted in endotracheal tube size (internal diameter of 7.5 or 8.0 mm, 1334/1509 [88.4% of intubations]; all intubated patients, 1530/1932 [79.2% of intubations]) or duration of intubation (median, 4.0 days; interquartile range [IQR], 1.9-7.9 days; all intubated patients, 3.2 [IQR, 1.2-7.1] days).

Primary Outcome
Among patients intubated for 24 hours or longer, rates of microbiologically confirmed VAP were 4.8% in patients receiving the silver-coated endotracheal tube (37/766 patients; 95% confidence interval [CI], 3.4%-6.6%) and 7.5% in those receiving the uncoated tube (56/743; 95% CI, 5.7%-9.7%) (\(P = .03\)), for a relative risk reduction in VAP incidence of 35.9% (95% CI, 3.6%-69.0%) (Table 2). Among all intubated patients, corresponding rates were

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**TABLE 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Randomized</th>
<th>Included in primary efficacy analysis</th>
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</thead>
<tbody>
<tr>
<td>Silver-coated tube</td>
<td>968</td>
<td>766</td>
</tr>
<tr>
<td>Uncoated tube</td>
<td>1005</td>
<td>743</td>
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</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Treatment</th>
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<td>1005</td>
<td>743</td>
</tr>
</tbody>
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3.8% (37/968 patients; 95% CI, 2.7%-5.2%) and 5.8% (56/964; 95% CI, 4.4%-7.5%) (P = .04), for a relative risk reduction in VAP incidence of 34.2% (95% CI, 1.2%-67.9%).

Of 264 patients with suspected VAP, 220 underwent BAL because of new radiographic infiltrate with qualifying signs (silver-coated, 69/129 [53%]; uncoated, 75/135 [56%]; P = .74) or physician suspicion (silver-coated, 34/129 [26%]; uncoated, 42/135 [31%]; P = .39). BAL fluid was obtained by nonbronchoscopic protected sampling catheter (silver-coated, 61/103 [59%]; uncoated, 83/117 [71%]), bronchoscopy (silver-coated, 36/103 [35%]; uncoated, 31/117 [26%]), or both methods (silver-coated, 69/129 [53%]; uncoated, 42/135 [31%]; P = .74) or physician suspicion (silver-coated, 34/129 [26%]; uncoated, 42/135 [31%]; P = .39). The most common pathogens present at a concentration of at least 10^6 colony-forming units/mL in BAL fluid were Staphylococcus aureus (silver-coated, 9; uncoated, 16), Pseudomonas aeruginosa (silver-coated, 8; uncoated, 11), and Enterobacteriaceae (silver-coated, 10; uncoated, 5). Twenty patients had polymicrobial infections (silver-coated, 7; uncoated, 13). No additional cases of VAP were suspected in patients intubated for less than 24 hours.

### Secondary Outcomes
In patients intubated for 24 hours or longer, the silver-coated endotracheal tube was associated with a 47.6% (95% CI, 14.6%-81.9%) relative risk reduction in VAP incidence within 10 days of intubation (P = .005) (Table 2) and with delayed occurrence of VAP (P = .005 by generalized Wilcoxon Test) (FIGURE 2). In all intubated patients, the relative risk reduction was 46.2% (95% CI, 12.6%-81.1% [P = .007]); the survival plot was nearly identical to that in patients intubated for 24 hours or longer (P = .005 by generalized Wilcoxon Test; data not shown).

No between-group differences were noted in median durations of intubation (both groups intubated ≥24 hours, 4.0 [IQR, 1.9-7.9] days [P = .59]; both groups all intubated, 3.2 [IQR, 1.2-7.1] days [P = .49]), ICU stay (both groups intubated ≥24 hours, 8.0 [IQR, 4.0-14.0] days [P = .92]; both groups all intubated, 7.0 [IQR, 3.0-13.0] days [P = .96]), or hospital stay (patients intubated with the silver-coated tube for ≥24 hours, 16.0 [IQR, 10.0-26.0] days; patients intubated with the uncoated tube for ≥24 hours, 16.0 [IQR, 10.0-27.0] days [P = .57]; both groups all intubated, 13.0 [IQR, 7.0-24.0] days [P = .93]). Mortality rates were 30.4% (233/766) in the group receiving the silver-coated tube and 26.6% (198/743) in the group receiving the uncoated tube (P = .11) (all intubated, 30.9% vs 27.3%; P = .08).

In a post hoc analysis of patients intubated for 24 hours or longer, microbiologically confirmed VAP was associated with an increase in the durations of intubation (VAP vs VAP-free patients, 10.0 [IQR, 6.2-15.1] vs 3.8 [IQR, 1.9-7.3] days [P < .001], ICU stay (18.0 [IQR, 11.0-29.0] vs 7.0 [IQR, 4.0-13.0] days [P < .001]), and hospital stay (27.0 [IQR, 16.0-31.0] vs 15.0 [IQR, 10.0-26.0] days [P < .001]). VAP was not associated with a higher mortality rate (26.9% [25/93 patients] vs 28.7% [406/1416] [P = .71]). No additional cases of VAP occurred in the group of all intubated patients.

### Regression Analyses
In multivariate logistic regression analyses of patients intubated for 24 hours or longer, the silver-coated endotracheal tube was associated with a 47.6% (95% CI, 14.6%-81.9%) relative risk reduction in VAP incidence within 10 days of intubation (P = .005) (Table 2) and with delayed occurrence of VAP (P = .005 by generalized Wilcoxon Test) (FIGURE 2). In all intubated patients, the relative risk reduction was 46.2% (95% CI, 12.6%-81.1% [P = .007]); the survival plot was nearly identical to that in patients intubated for 24 hours or longer (P = .005 by generalized Wilcoxon Test; data not shown).

### Table 1. Demographic and Other Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intubated ≥24 h</th>
<th>All Intubated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>457 (59.7)</td>
<td>566 (58.5)</td>
</tr>
<tr>
<td>Female</td>
<td>416 (56.9)</td>
<td>551 (57.2)</td>
</tr>
<tr>
<td>Age, mean (SD) [range], y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60.9 (15.7) [19-98]</td>
<td>61.5 (15.4)</td>
<td>62.2 (15.2)</td>
</tr>
<tr>
<td>62.0 (15.4) [18-98]</td>
<td>62.2 (15.2)</td>
<td>62.2 (15.2)</td>
</tr>
<tr>
<td>APACHE II score, mean (SD) [range]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.4 (7.4) [4-49]</td>
<td>21.5 (7.5) [3-65]</td>
<td>21.6 (7.5) [3-65]</td>
</tr>
<tr>
<td>Risk factors for VAP within 30 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional dependency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>132 (17.2)</td>
<td>133 (13.7)</td>
</tr>
<tr>
<td>Impaired sensorium</td>
<td>121 (15.8)</td>
<td>122 (12.6)</td>
</tr>
<tr>
<td>COPD</td>
<td>89 (11.6)</td>
<td>89 (9.2)</td>
</tr>
<tr>
<td>Emergency surgery/trauma</td>
<td>77 (10.1)</td>
<td>77 (8.0)</td>
</tr>
<tr>
<td>Chronic steroids use</td>
<td>61 (8.0)</td>
<td>61 (6.3)</td>
</tr>
<tr>
<td>None</td>
<td>141 (18.4)</td>
<td>143 (14.8)</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>184 (24.6)</td>
<td>198 (21.2)</td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>455 (59.4)</td>
<td>464 (50.7)</td>
</tr>
<tr>
<td>Patient location at intubation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical ICU</td>
<td>154 (20.1)</td>
<td>179 (18.5)</td>
</tr>
<tr>
<td>Other ICU or burn unit</td>
<td>310 (40.5)</td>
<td>338 (34.9)</td>
</tr>
<tr>
<td>Operating or recovery room</td>
<td>240 (32.5)</td>
<td>298 (30.8)</td>
</tr>
<tr>
<td>Emergency department</td>
<td>34 (4.4)</td>
<td>43 (4.4)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.2)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Multiple locations</td>
<td>10 (1.3)</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>89 (9.2)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

*p > .05 for all between-group differences except for COPD (P = .007 for patients intubated ≥24 hours; P = .02 for all intubated patients).

*a Based on assessment by a research nurse and choice of options listed in the case report form.

*b Defined as receiving high-dose steroids for more than 2 weeks, presence of human immunodeficiency virus antibody, chemotherapy within 45 days, chemotherapy-induced neutropenia, immunosuppression for organ transplantation, or other.
longer (Table 3), treatment group was associated with reduced risk of developing VAP at any time (odds ratio for silver-coated vs uncoated, 0.52; 95% CI, 0.33-0.82 [P = .005]) and within 10 days of intubation (odds ratio, 0.44; 95% CI, 0.26-0.73 [P = .001]). In the Cox regression analysis, treatment group was associated with delayed time to occurrence of VAP (hazard ratio, 0.55; 95% CI, 0.33-0.82 [P = .005]) and within 10 days (hazard ratio, 0.26; 95% CI, 0.13-0.52 [P = .001]). The analyses of all intubated patients showed nearly identical results (Table 3).

Safety

There were no statistically significant between-group differences in the frequency and severity of adverse events, including those unrelated to the endotracheal tube or intubation procedure (Table 4). Fifty-nine adverse events were reported as definitely related to the endotracheal tube (silver-coated, 39; uncoated, 38). Seventy-four adverse events were definitely related to the intubation procedure (silver-coated, 39; uncoated, 35).

COMMENT

The silver-coated endotracheal tube was associated with a statistically significant reduction in the incidence of VAP based on rigorous diagnostic criteria requiring microbiological confirmation. As expected, most episodes occurred during the first 10 days of intubation. More importantly, the silver-coated tube had its greatest impact during the first 10 days of intubation.

Figure 2.

Kaplan-Meier Analyses of Occurrence of Microbiologically Confirmed Ventilator-Associated Pneumonia (VAP) in Patients Intubated for 24 Hours or Longer

Table 2. Incidence of Microbiologically Confirmed Ventilator-Associated Pneumonia (VAP)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Microbiology\textsuperscript{b}</th>
<th>Evaluable Patients With VAP, No./Total (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>9/16</td>
</tr>
<tr>
<td>Methicillin-resistant S aureus</td>
<td>3/7</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>8/11</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>10/5</td>
</tr>
<tr>
<td>Yeast</td>
<td>5/7</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>4/7</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>3/3</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>1/5</td>
</tr>
<tr>
<td>Other\textsuperscript{c}</td>
<td>5/17</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
\textsuperscript{a}Patients with at least 10\textsuperscript{3} colony-forming units/mL in bronchoalveolar lavage fluid.
\textsuperscript{b}Twenty patients had polymicrobial infections. In the group receiving the silver-coated endotracheal tube, 6 patients had 2 microorganisms and 1 patient had 3. In the group receiving the uncoated tube, 11 patients had 2 microorganisms and 2 patients had 3.
\textsuperscript{c}Other microorganisms in the group receiving the silver-coated endotracheal tube were normal flora (n = 4) and Stenotrophomonas maltophilia (n = 1). Other microorganisms in the group receiving the uncoated tube were normal flora (n = 8), S maltophilia (n = 2), Nocardia (n = 2), coagulase-negative staphylococci (n = 3), vancomycin-resistant enterococcus (n = 1), and Burkholderia cepacia (n = 1).

Our findings add to those of previous studies\textsuperscript{27,28} suggesting that controlling colonization and biofilm formation may reduce the risk of VAP. The silver-coated endotracheal tube reduced the bacterial burden in the trachea, in the distal airways, and on endotracheal tubes in dogs challenged with P aeruginosa.\textsuperscript{27} Silver sulfadiazine-coated endotracheal tubes also reduced respiratory tract bacterial colonization in sheep.\textsuperscript{36} Similarly, the silver-

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coated tube reduced the bacterial burden in tracheal aspirates and delayed bacterial colonization on endotracheal tubes in a randomized feasibility study of 121 adults requiring mechanical ventilation. In addition, silver-coated tubes were less likely to have mucus covering the surface or obstructing the lumen. The magnitude of some benefits was consistent across studies. For example, the silver-coated tube was associated with 37% lower P aeruginosa tube concentrations in dogs, 40% fewer days of tube colonization in the feasibility study, and a 36% lower incidence of VAP in the current study. The current study also demonstrated a reduced incidence of VAP caused by potentially highly resistant pathogens, including methicillin-resistant S aureus, P aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, and Burkholderia cepacia.

Only one other endotracheal tube has been evaluated for its effect on VAP in a large number of patients. Subglottic secretion drainage using this tube was associated with a reduced risk of VAP in a meta-analysis; however, heterogeneity among the 5 studies published between 1992 and 2002, restriction of patients to those requiring 72 hours or more of intubation, and use of different diagnostic criteria preclude comparison with our findings. Furthermore, subglottic suction combined with semirecumbent positioning failed to show a benefit, as measured by tracheal colonization in a more recent study. This tube and the silver-coated tube used in the current study are not comparable because, unlike the silver-coated tube, the tube enabling subglottic secretion drainage requires active participation by the clinician and routine maintenance to ensure patency of the suction lumen.

| Table 3. Multivariate Analyses of Risk Factors for Developing Ventilator-Associated Pneumonia (VAP) |
| Variable | OR (95% CI) | P Value | OR (95% CI) | P Value | OR (95% CI) | P Value | OR (95% CI) | P Value |
| Treatment group, silver-coated vs uncoated tube | 0.62 (0.32-0.82) | .005 | 0.64 (0.36-0.82) | .001 | 0.55 (0.29-0.82) | .006 | 0.51 (0.32-0.82) | <.001 |
| Antibiotic therapy at intubation, yes vs no | 0.39 (0.22-0.70) | .001 | 0.34 (0.19-0.61) | <.001 | 0.45 (0.22-0.74) | .002 | 0.39 (0.19-0.61) | <.001 |
| APACHE II score $\geq 20$ | 0.50 (0.32-0.80) | .003 | 0.53 (0.32-0.82) | .004 | 0.48 (0.29-0.80) | .003 | 0.48 (0.29-0.82) | .004 |
| Enteral nutrition, yes vs no | 5.03 (2.22-11.40) | <.001 | 5.67 (2.35-13.68) | <.001 | 3.16 (1.42-7.06) | .005 | 5.10 (1.25-11.58) | <.001 |
| Sex, male vs female | 1.62 (1.01-2.60) | .04 | NA | NA | 1.47 (0.96-2.27) | .08 | 1.62 (1.01-2.60) | .04 |
| Duration of intubation, d | 1.13 (1.09-1.17) | <.001 | 1.10 (1.06-1.14) | <.001 | 1.05 (1.02-1.09) | <.001 | 1.10 (1.06-1.14) | <.001 |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; HR, hazard ratio; NA, not applicable; OR, odds ratio. The following risk factors were eliminated from final models because $P > .10$: hospital duration before study, oral care, continuous sedation, coma, chronic obstructive pulmonary disease, emergency surgery/trauma, and age.

From multiple logistic regression analysis.

From Cox regression analysis.

Sex was eliminated from the analysis of VAP incidence within 10 days of intubation.

| Table 4. Adverse Events in All Intubated Patients |
| Adverse Event | Silver-Coated Tube (n = 968) | Uncoated Tube (n = 964) |
| Events, No. | Patients, % | Events, No. | Patients, % | Value |
| Possibly related to endotracheal tube | 196 (122 (12.6) | 149 (111 (11.5) | .46 |
| Definitely related to endotracheal tube | 21 (18 (1.9) | 38 (27 (2.8) | .17 |
| Unanticipated | 11 (10 (1.0) | 22 (15 (1.6) | .31 |
| Cough and other respiratory disorders | 2 (2 (0.2) | 7 (6 (0.6) | .15 |
| Dysphagia and other gastrointestinal tract disorders | 2 (2 (0.2) | 4 (4 (0.4) | .41 |
| Bacteremia, sepsis, and other infections | 2 (1 (0.1) | 3 (2 (0.2) | .56 |
| Device malfunction and other procedural complications | 2 (2 (0.2) | 1 (1 (0.1) | .57 |
| Other | 3 (3 (0.3) | 7 (7 (0.7) | .20 |

In the group receiving the silver-coated tube, other events were abnormal breath sounds (n = 1), anxiety (n = 1), and skin disorder (n = 1). In the group receiving the uncoated tube, other events were catheter-related complication (n = 1), edema (n = 1), decreased oxygen (n = 1), atrial flutter (n = 1), headache (n = 1), and acute renal failure (n = 1).
significant increases in durations of intubation and hospitalization. Other studies have demonstrated that VAP is associated with substantial morbidity and mortality.1,3 The burden averaged more than an additional $40 000 per inpatient in an analysis of more than 800 patients with VAP and 2000 matched control patients requiring mechanical ventilation.3 The additional charges associated with VAP resulted from prolonging the mean durations of mechanical ventilation from 4.7 to 14.3 days, of ICU stay from 5.6 to 11.7 days, and of hospital stay from 14.0 to 25.5 days.

The estimated number of patients needed to treat with the silver-coated endotracheal tube to prevent 1 case of VAP is approximately 37 (95% CI, 19-369), based on patients intubated for 24 hours or longer, and the absolute difference in the primary outcome was 2.7% (95% CI, 0.3%-5.2%). While these results may appear modest and suggest that the silver-coated tube may have the greatest benefit in high-risk patients, the results probably reflect the low incidence of VAP in our study population. Rates of VAP may have been related to the requirement for informed consent, which precluded enrolling some patients needing emergent intubation. Additionally, the 4-day median duration of intubation suggests that patients requiring longer durations, and thus at greater risk for VAP, were not as readily enrolled. These factors should be considered in interpreting our results. Another factor that may have contributed to the low VAP rate was study participation resulting in increased awareness and possibly increased adherence to other local infection-control measures over the 3-year study period. Nevertheless, this is the first intervention demonstrated to reduce VAP incidence that does not require more effort or supervision from clinicians providing bedside care, which is characteristic of other approaches (eg, elevating the head of the bed, subglottic secretion suctioning, selective digestive decontamination).

We found no overt safety issues with the silver-coated endotracheal tube. The distribution and pattern of adverse events were similar between treatment groups.

Our study had several additional findings that merit consideration, including some that may be attributable to study limitations. The lack of between-group differences in duration of ICU stay, mortality, and other secondary outcomes has been shown in other interventional studies.30,43 The inability to detect between-group differences in secondary outcomes, including mortality, may have been related to the low VAP rate in the group receiving the uncoated tube, which was approximately half the expected rate of 15%. We also did not examine other secondary outcomes, such as initiation of post-BAL antibiotic therapy for VAP. Many different diagnostic criteria for VAP are used in clinical practice. We chose standard criteria8,44 as triggers for further evaluation and required microbiological confirmation of VAP. The coating on the endotracheal tube was not likely to influence culture results, because the methods for performing BAL bypassed the tube and allowed direct sampling of the lower respiratory tract, as demonstrated in our animal study.27 The study could not be double-blinded, but microbiology samples and personnel were blinded. A further potential design weakness was use of a small, fixed block size stratified by center. Variable block size and double-blinding could have minimized any potential for investigator bias.

Another limitation is that other factors may have contributed to between-group differences in VAP rates. First, BAL quantitative culture results could have been influenced by introducing new antibiotics before obtaining culture specimens. This appears unlikely, because the number of patients receiving antibiotics when BAL specimens were obtained was similar between groups.

Second, chronic obstructive pulmonary disease was more common in the group receiving the uncoated tube. This risk factor may have contributed to the occurrence of VAP despite not being significant in our regression analysis.

Third, 5 of 56 episodes of VAP (8.9%) in the group receiving the uncoated tube were diagnosed on the first day of mechanical ventilation, compared with none in the group receiving the silver-coated endotracheal tube. Most early episodes of VAP are due to massive inoculation of the lower respiratory tract by virulent bacteria that overwhelm lower respiratory host defenses. One explanation is offered by our dog study, which demonstrated significant reductions in histologically confirmed VAP among mechanically ventilated dogs challenged with P aeruginosa at intubation.27 The silver coating may have countered inoculum effects, as suggested by recent animal and in vitro microbiological studies.30,45

Fourth, the difference in VAP rates was marginally significant for all intubated patients in the univariate analysis, suggesting that a few additional episodes of VAP in the group receiving the silver-coated tube may have resulted in statistical nonsignificance. Similarly, the occurrence of VAP after 7 days of intubation was low, limiting our ability to assess this subset. Nevertheless, between-group differences were statistically significant in univariate analyses of VAP incidence in patients intubated for 24 hours or longer and in all intubated patients, of VAP within 10 days, and of time to occurrence. Regression analyses confirmed that treatment group remained significant for each outcome after adjusting for other variables.

A key issue in evaluating new preventive strategies is how care in the group receiving the uncoated tube was managed and how preventive guidelines were implemented in the participating centers. Our study protocol did not standardize prevention strategies, which could have influenced between-group VAP rates. We intentionally allowed participating sites to follow local practices to allow evaluation of new technology in conjunction with other prevention strategies. Although we encouraged consistency through
Finally, we observed that higher severity-of-illness scores had a protective effect against developing VAP. This may have been related to higher short-term mortality of patients with APACHE II scores of 20 or greater, which reduced their propensity to develop VAP.

In conclusion, the results of this large, randomized, multicenter study demonstrated that the silver-coated endotracheal tube significantly reduced the incidence of microbiologically confirmed VAP and had its greatest benefit during the peak time of VAP occurrence, without any notable adverse events. The silver-coated endotracheal tube appears to offer a unique approach because it is the first intervention that becomes user-independent after intubation, requiring no further action by the clinician.

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REFERENCES

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