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Preventing Ventilator-Associated Pneumonia Could Silver-Coated Endotracheal Tubes Be the Answer?

Jean Chastre, MD

VENTILATOR-ASSOCIATED PNEUMONIA (VAP) IS THE intensive care unit (ICU)-associated infection most frequently acquired among patients receiving mechanical ventilation and is responsible for approximately 50% of all antibiotics prescribed in this setting.¹⁻³ Because VAP has been associated with increased morbidity, longer hospital stays, increased health care costs, and higher mortality rates, prevention of this infection is a major challenge for all ICU personnel.^{1,2,4,5} Numerous preventive strategies have been tested, and updated recommendations have been published.⁶⁻⁹ However, evaluation of the effect of such interventions is a complex issue.

Three methodological difficulties limit the value of measuring the potential efficacy of strategies to prevent VAP. Specifically, these are difficulties in (1) obtaining an accurate diagnosis of VAP, because only patients who develop true VAP are likely to benefit from preventive measures; (2) precisely determining the impact of prophylactic measures on the overall mortality of a general ICU population to identify preventable deaths directly attributable to VAP among all deaths occurring in a population of ventilated ICU patients; and (3) assessing the consequences of a preventive measure on a potentially pathogenic mechanism—a surrogate outcome—to determine the exact role played by prevention, reduction, or modulation of tracheal colonization in modifying the development of VAP.

In this issue of *JAMA*, Kollef and colleagues¹⁰ report the results of the North American Silver-Coated Endotracheal Tube (NASCENT) study, which examined the potential efficacy of a new endotracheal tube for preventing VAP in ICU patients expected to require mechanical ventilation for 24 hours or longer. This new endotracheal tube, which is otherwise similar to standard devices, is coated with silver ions microdispersed in a proprietary polymer and thus could potentially reduce the VAP rate by preventing biofilm formation at its surface and hampering respiratory tract bacterial colonization, both of which are key predisposing factors to infection of the pulmonary parenchyma.

Several studies have clearly documented that most cases of VAP result from the aspiration of pathogens that have colonized the mucosal surfaces of the oropharyngeal cavity.^{2,11} The presence of an endotracheal tube not only compromises the natural barrier between the oropharynx and trachea but also may facilitate the entry of bacteria into the lung by pooling and leaking of contaminated secretions around the cuff. This mechanism occurs in most intubated patients, whose supine position may facilitate occurrence of VAP.¹² Moreover, biofilm formation on the inner and outer surfaces of the endotracheal tube provides a protected environment for pathogens. Bacterial aggregates in biofilm dislodged during suctioning might not be eradicated by antibiotics or effectively cleared by host immune defenses, thereby constituting dangerous inoculums for the lung. Preliminary data obtained in animal models and from small randomized human studies also support the hypothesis that an endotracheal tube coated externally and internally with a potent antiseptic product such as silver could exert a sustained antimicrobial effect within the proximal airways and block biofilm formation at its surface.¹³⁻¹⁵

To evaluate the usefulness of silver-coated endotracheal tubes in clinical practice, Kollef et al¹⁰ performed a randomized, multicenter, single-blind trial in 1932 patients who required endotracheal intubation and mechanical ventilation at 54 centers in North America and analyzed whether use of a silver-coated endotracheal tube led to fewer VAP episodes, as assessed by quantitative culture results of distal respiratory secretions obtained by bronchoalveolar lavage. The authors conducted this trial using stringent, carefully defined microbiological and clinical criteria for diagnosing VAP, avoiding the major bias, ie, an inaccurate and nonspecific diagnostic methodology.

Based on their findings for the 1509 patients intubated for more than 24 hours who thus fulfilled the predefined criteria of a modified intention-to-treat analysis, Kollef et al¹⁰ conclude that the new device was able to lower the VAP frequency from 7.5% for the control group to 4.8% for the group receiving the silver-coated endotracheal tube. These findings correspond to a relative risk reduction of 35.9% and

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an absolute risk reduction of 2.7%, suggesting that 37 patients had to be treated with the silver-coated tube to prevent 1 case of VAP (95% confidence interval [CI], 19-369). However, use of the silver-coated tube did not reduce mortality rates, the duration of intubation, duration of ICU or hospital length of stay, or the frequency or severity of adverse effects.

Kollef et al¹⁰ prudently acknowledge that their findings may have some limitations. Due to the difficulties inherent in conducting such a trial, in which many patients could not be included because informed consent was impossible within the time frame needed for emergency intubation, only a small fraction of the potentially eligible patients were randomized, thereby threatening the external validity of the trial and its clinical relevance. Also, 3 additional episodes of VAP in the group receiving the silver-coated tube would have sufficed to render the trial statistically inconclusive.

This absence of robustness of the results is particularly worrisome for 3 reasons. First, the ICU investigators were not blinded, which could have introduced a bias in favor of the new device.

Second, quantitative culture results from bronchoalveolar lavage could be markedly negatively influenced by the introduction of new antibiotics after the onset of symptoms and signs of infection but before obtaining respiratory secretions—ie, some respiratory samples from some patients might have been collected after the introduction of antibiotics, potentially artificially reducing the VAP rate of the group to which these patients were randomized. Lower thresholds obtained from quantitative cultures may also represent true infections in some cases, especially when these techniques are not used properly—ie, when performed after introduction of new antibiotics or modification of prior antimicrobial treatment.¹

Third, a statistically significant imbalance in the proportion of patients with preexisting chronic obstructive pulmonary disease existed between the 2 groups, favoring the group receiving the silver-coated endotracheal tube. This situation is unfortunate, because the disease is a recognized risk factor for VAP, as demonstrated in many studies, though it was not confirmed in this trial using regression analysis. Moreover, the investigators did not evaluate antibiotics specifically given to treat VAP, and therefore it remains unknown whether patients randomized to receive the silver-coated tube received fewer antibiotics during the study period than did randomized controls—which should have been the case if the new device was effectively able to lower VAP by a relative rate of 35.9%.

Based on the results of this trial, should clinicians reconsider guidelines for VAP prevention and use a silver-coated endotracheal tube in all patients requiring intubation and mechanical ventilation in the ICU? The answer is probably yes for the subset of patients at very high risk of developing early-onset VAP, such as neurologically impaired patients or trauma patients, because the greatest effect of

the intervention appeared to occur during the first 10 days of mechanical ventilation and was clinically relevant, with minimal effect on clinician workload. Indeed, the benefit of the silver-coated tube should be greatest when the risk of developing VAP is high. The answer is not so obvious for other patients, particularly those requiring prolonged mechanical ventilation. As Kollef et al¹⁰ acknowledge, the number of late-onset VAP cases occurring after 7 days of mechanical ventilation in their study was small, limiting their ability to demonstrate the efficacy of silver-coated endotracheal tubes in the setting of prolonged mechanical ventilation. While these late-onset infections are difficult to prevent, they also are difficult to treat and affect prognosis the most.

One key issue in every trial evaluating a new preventive strategy is how the care of patients in the control group was managed and how standard precautions for preventing pneumonia, as recommended by current guidelines, were implemented in the participating ICU. Because respiratory tract colonization among ICU patients is complex, corresponding to a mix of self-colonization and cross-transmission, many ICUs are now using multifaceted and multidisciplinary programs aimed at preventing VAP. Such care bundles make it possible to introduce evidence-based preventive measures, including appropriate nursing staff levels,¹⁶ hand hygiene with alcohol,¹⁷ weaning protocols and daily interruption of sedation,¹⁸ oral care with chlorhexidine,^{19,20} restrictive transfusion policy,²¹ and keeping patients receiving enteral nutrition in a semirecumbent position.²² All of these measures can be consistently applied to all patients in a coordinated way. Recent experience confirms the positive effects of these approaches, and it is not known whether the use of the silver-coated endotracheal tube will further decrease the VAP rate when such preventive measures are in place.^{23,24} According to the results of randomized clinical studies and meta-analyses, significantly fewer central venous catheter-related infections were reported when antiseptic- or antimicrobial-coated catheters were used; globally, however, the effect of these devices was later demonstrated to be within the same ranges as those of the educational programs.²⁵⁻²⁷

Important uncertainties exist regarding the exact benefit of silver-coated endotracheal tubes. Consequently, silver-coated tubes should not be viewed as the definitive answer for VAP prevention, and, until additional data confirm the clinical effectiveness and cost benefit of these devices, their use should be restricted to high-risk patients treated in ICUs with benchmark value-based infection rates that remain above institutional goals despite implementation of a comprehensive strategy of usual preventive measures to prevent VAP. In the United States, the Centers for Medicare & Medicaid Services has proposed stopping hospital reimbursements for care made necessary by preventable complications, including nosocomial infections.²⁸ Although this

plan may have the desirable consequences of improving the quality of care, it also may penalize hospitals that admit high-risk patients and inadvertently encourage institutions to underreport VAP or to overuse antibiotics, thereby favoring dissemination of multidrug-resistant microorganisms. This possibility further underscores the need to carefully evaluate all new technologies potentially aimed at preventing VAP against what represents best clinical practices.

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