

LETTERS TO THE EDITOR

Prevention of Ventilator-Associated Pneumonia by Use of Oral Chlorhexidine

To the Editor—We read with interest the article by Tantipong et al.¹ on the use of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia (VAP). We believe that their study has some important limitations and that the authors' conclusion that oral chlorhexidine is an effective and safe method for VAP prevention is not supported by the results.

In their study, some patients received ventilation for less than 48 hours, the population was not homogeneous, and the randomization procedure was not adequate. The mean duration of mechanical ventilation was approximately 5 days, but only 43% of patients in the test group and 50% of patients in the control group received ventilation for more than 48 hours, a period that, if not completed, is usually considered an exclusion criterion in the majority of trials on VAP prevention. Approximately 60% of patients admitted to their study were adults who received ventilation in intensive care units (ICUs) (mainly surgical ICUs), whereas 40% received ventilation in general medical wards. Although the mean Acute Physiology and Chronic Health Evaluation II score was not significantly different among the 2 arms, it is highly likely that patients who received ventilation in general medical wards were in less "critical" condition than those treated in ICUs. Moreover, the care of a patient who receives ventilation may be different in the general ward than in the ICU, all wards did not change their regular protocols, parenteral antibiotic policy was not reported, semirecumbency was maintained only "if possible," and the degree of semirecumbency was not assessed. Therefore, the study results seem to not be generalizable to the high-risk ICU population. Finally, randomization according to patient sex is not an adequate method of randomization, the study was not blinded, and it

is not clear whether consecutive patients were enrolled. All these issues may have influenced the results and should be acknowledged by the authors.

The authors' claim that oral decontamination with 2% chlorhexidine solution is an effective method for reducing VAP is not supported by the results and may be misleading for the reader. Although use of chlorhexidine reduced the risk of VAP by approximately 55% in the overall population and among patients who received mechanical ventilation for more than 2 days, this reduction was not statistically significant, because both relative-risk (RR) calculations had large 95% confidence intervals (CIs) (RR, 0.43 [95% CI, 0.16–1.17] for study patients who received mechanical ventilation and oral decontamination and RR, 0.45 [95% CI, 0.16–1.23] for patients who received mechanical ventilation for more than 2 days). The study showed a significant, albeit borderline ($P = .04$), reduction in the number of episodes of pneumonia per 1,000 ventilator-days, but this reduction was not statistically significant ($P = .06$) when the authors evaluated only patients who received mechanical ventilation for more than 48 hours, which is an acceptable period for the diagnosis of VAP.

The authors stated that all VAP cases were due to gram-negative bacilli, but they were unable to specify the type of microorganism. Many different microorganisms are included in the category of gram-negative bacilli, which may have a variety of associated morbidity and mortality. *Haemophilus influenzae*, a gram-negative bacillus that belongs to the "normal" oropharyngeal flora, is readily cleared by parenteral antibiotics and usually causes VAP soon after the initiation of mechanical ventilation.² Aerobic gram-negative bacilli of the "abnormal flora," such as *Pseudomonas*, *Klebsiella*, *Serratia*, *Enterobacter*, *Citrobacter*, *Proteus*, and *Acinetobacter* species, may cause VAP after 1 week in the ICU and are associated with increased morbidity and mortality.³

The authors assessed the safety of oral decontamination with 2% chlorhexidine solution by evaluating the irritation

TABLE. Data Collected During the Admission Screening of Patients for Extended-Spectrum β -Lactamase-Producing Enterobacteriaceae in 4 Intensive Care Units (ICUs) at the University Medical Center Freiburg, Germany, 2007

ICU	Period	Proportion (%) of patients		
		Screened, with colonization or infection detected for the first time	Admitted, who were infected or colonized	With rectal colonization, who subsequently developed infection
A	Oct 1–Dec 31	3/48 (6.3)	4/137 (2.9)	3/3 (100)
B	Oct 1–Dec 31	6/67 (9.0)	14/230 (6.1)	1/8 (12.5)
C	Aug 15–Dec 31	14/463 (3.0)	25/1,057 (2.4)	5/15 (33.3)
D	Oct 1–Dec 31	6/177 (3.4)	9/250 (3.6)	0/9 (0)
Total		29/755 (3.8)	52/1,674 (3.1)	9/35 (25.7)

of the oropharyngeal mucosa. Again, they stated that the method was safe, ignoring their own findings of a significant increase in mild mucosa irritation in the test group.

Finally, the authors performed a meta-analysis, which included their study and that of Koeman et al.,⁴ that demonstrated a significant reduction in the rate of VAP associated with the use of chlorhexidine (pooled RR, 0.53 [95% CI, 0.31–0.90]). Four meta-analyses of randomized, controlled trials of oral antiseptics have been published.^{5–8} Two of these meta-analyses failed to show any significant reduction in pneumonia rates,^{5,6} and the other 2 revealed a significant reduction.^{7,8} However, these positive results should be interpreted with caution for the following reasons. (1) More than two-thirds of patients included in these meta-analyses were cardiac surgery patients who received a very short period of mechanical ventilation and therefore had a low risk for developing VAP; those studies included reported the incidence of nosocomial pneumonia, not that of VAP⁹ (eg, “most of the patients received only 2 doses of the oral rinse agents because extubation routinely occurred within 4–8 hours after surgery” [p 2468]). (2) In studies including surgical patients, perioperative prophylaxis with parenteral antibiotics was always given. (3) Not all consecutive patients were enrolled in some studies that focused on dental plaque instead of the oropharynx, which excluded edentulous patients. (4) There were different definitions of respiratory tract infection, because some studies reported the incidence of lower respiratory tract infections, including tracheobronchitis, whereas other studies included only incidences of VAP. (5) Oral chlorhexidine was administered using multiple application forms (ie, solution, spray, gel, and paste) and a variety of concentrations (0.12%–2%), dosages (1–4 doses per day), and durations (ie, once, for 10 days, or until extubation). A recent meta-analysis concluded that use of oral chlorhexidine might be effective in preventing lower respiratory tract infections in patients receiving mechanical ventilation for up to 48 hours, although its impact in preventing late-onset VAP requires further research.⁸ Remarkably, none of those meta-analyses, or the study by Tantipong et al.¹ demonstrated any impact on mortality.

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this study.

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Reply to Silvestri et al.

To the Editor—We welcome the comments of Silvestri et al.¹ regarding our article² on the effectiveness of chlorhexidine for the prevention of ventilator-associated pneumonia (VAP). We offer the responses.

We included all patients who underwent mechanical ventilation, because we wanted to determine the effectiveness of 2% chlorhexidine solution for the prevention of VAP in all patients who underwent mechanical ventilation, not only the patients who underwent it for more than 48 hours. Therefore, our study results should be more generalizable than the results of a study that included only the patients who received mechanical ventilation for more than 48 hours.

The patients who received mechanical ventilation in general medical wards were not in less critical condition than those who received mechanical ventilation in intensive care units. Many critically ill patients had to stay in general medical wards because intensive care units had limited capacity, and beds in intensive care units were not available for all patients who received mechanical ventilation in developing countries. Therefore, the study population should have been homogeneous.

Furthermore, we were unable to perform a double blind study, because the odor of chlorhexidine is very distinctive