

ORIGINAL ARTICLE

Randomized Controlled Trial and Meta-analysis of Oral Decontamination with 2% Chlorhexidine Solution for the Prevention of Ventilator-Associated Pneumonia

Hutsaya Tantipong, MD; Chantana Morkchareonpong, MD; Songyod Jaiyindee, MD; Visanu Thamlikitkul, MD

OBJECTIVE. To determine the effectiveness of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia (VAP).

DESIGN. Randomized controlled trial and meta-analysis.

SETTING. A tertiary care university hospital in Bangkok, Thailand.

PARTICIPANTS. Adult patients who received mechanical ventilation and who were hospitalized in intensive care units and general medical wards.

METHODS. The patients were randomized to receive oral decontamination with 2% chlorhexidine solution or normal saline solution 4 times per day until their endotracheal tubes were removed. The outcome measures were the development of VAP and oropharyngeal colonization with gram-negative bacilli. Meta-analysis was performed by combining the results of the present study with those from another randomized controlled trial that also used a 2% chlorhexidine formulation for oral decontamination.

RESULTS. The characteristics of the patients in the chlorhexidine group ($n = 102$) and the normal saline group ($n = 105$) were not significantly different. The incidence of VAP in the chlorhexidine group was 4.9% (5 of 102), and the incidence in the normal saline group was 11.4% (12 of 105) ($P = .08$). The rate of VAP in the chlorhexidine group was 7 episodes per 1,000 ventilator-days, and the rate in the normal saline group was 21 episodes per 1,000 ventilator-days ($P = .04$). Irritation of the oral mucosa was observed in 10 (9.8%) of the patients in the chlorhexidine group and in 1 (0.9%) of the patients in the normal saline group ($P = .001$). Oropharyngeal colonization with gram-negative bacilli was either reduced or delayed in the chlorhexidine group. Overall mortality of the patients did not differ significantly between the groups. Meta-analysis of 2 randomized controlled trials revealed an overall relative risk of VAP for patients in the chlorhexidine group of 0.53 (95% confidence interval, 0.31-0.90; $P = .02$).

CONCLUSION. Oral decontamination with 2% chlorhexidine solution is an effective and safe method for preventing VAP in patients who receive mechanical ventilation.

Infect Control Hosp Epidemiol 2008; 29:131-136

Nosocomial pneumonia among patients receiving mechanical ventilation, also called ventilator-associated pneumonia (VAP), is an important nosocomial infection worldwide, which leads to increases in length of hospital stay, healthcare costs, and mortality.¹⁻⁵ The rate of VAP in Siriraj Hospital (Bangkok, Thailand) was 14 episodes per 1,000 ventilator-days, and 90% of the causative agents were gram-negative bacilli.⁵ An episode of VAP in Siriraj Hospital increased the length of a patient's hospital stay by a mean of 13.2 days, increased the cost of antimicrobial therapy by a mean of \$400, and contributed to a 20% increase in mortality.⁵ Oral and dental colonization with pathogens in patients who received mechanical ventilation is associated with the development of VAP.^{6,7} Therefore, oral decontamination with antibiotics and/

or antiseptics has been attempted for the prevention of pneumonia in these patients.

A meta-analysis of good-quality randomized controlled trials⁸⁻¹¹ of oral decontamination with antibiotics for the prevention of pneumonia in patients who received mechanical ventilation revealed that topical antibiotic therapy was not an effective method of preventing VAP. Randomized controlled trials of oral decontamination showed that topical use of 0.12% or 0.2% chlorhexidine solution was effective for preventing pneumonia in patients who underwent cardiothoracic surgery.⁸⁻¹⁷ The Centers for Disease Control and Prevention guideline for the prevention of healthcare-associated pneumonia published in 2004 made no recommendation on routine oral decontamination with chlorhexidine solution for

From the Department of Medicine (V.T., H.T., C.M., S.J.), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Received July 30, 2007; accepted October 12, 2007; electronically published December 31, 2007.

© 2007 by The Society for Healthcare Epidemiology of America. All rights reserved. 0899-823X/2008/2902-0006\$15.00. DOI: 10.1086/526438

the prevention of healthcare-associated pneumonia in critically ill patients and other patients who received mechanical ventilation and were at high risk for pneumonia.¹⁸

In 2006, we initiated a randomized controlled trial to determine the effectiveness and safety of using a higher concentration of chlorhexidine in solutions used for oral decontamination to prevent VAP. However, 3 meta-analyses published in 2007 revealed that oral decontamination with chlorhexidine solution reduced pneumonia in patients who received mechanical ventilation.¹⁹⁻²¹ These meta-analyses included a randomized controlled trial published in 2006 that used 2% chlorhexidine solution for oral decontamination.²² They found that 2% chlorhexidine oral decontamination was marginally effective for the prevention of pneumonia in patient who received mechanical ventilation, with a relative risk (RR) of 0.58 (95% confidence interval [CI], 0.31-1.09). Hence, we also performed a meta-analysis that included only the randomized controlled trials that evaluated oral decon-

tamination with 2% chlorhexidine to prevent pneumonia in patients who received mechanical ventilation.

METHODS

Randomized Controlled Trial

The study was approved by the Ethics Committee on Human Research, Faculty of Medicine Siriraj Hospital. The study was conducted from January 2006 through March 2007 at Siriraj Hospital, which is a 2,300-bed, tertiary care university hospital.

Eligible patients were adults aged 18 years or older who were hospitalized in intensive care units (a total of 36 beds) or general medical wards (a total of 240 beds) at Siriraj Hospital and who received mechanical ventilation. Patients who had pneumonia at enrollment or who had a chlorhexidine allergy were excluded. Each eligible patient was randomized to the chlorhexidine group or the normal saline group by

TABLE 1. Demographic and Clinical Characteristics of 207 Study Patients Who Received Mechanical Ventilation and Oral Decontamination

Characteristic	Chlorhexidine group (n = 102)	Normal saline group (n = 105)	P
Age, mean ± SD, years	56.5 ± 20.1	60.3 ± 19.1	.15
Sex			
Male	50 (49.1)	51 (48.6)	.78
Female	52 (50.9)	54 (51.4)	
Ward			
Surgical ICU	50 (49.0)	51 (48.6)	.99
General medical ward	40 (39.2)	42 (40.0)	
Medical ICU	12 (11.8)	12 (11.4)	
Underlying disease			
Yes	75 (73.5)	75 (71.4)	.75
No	27 (26.5)	30 (28.6)	
Reason for endotracheal intubation			
Upper airway obstruction	15 (14.7)	23 (21.9)	.21
Oxygenation failure	66 (64.7)	61 (58.0)	.39
Airway protection	31 (30.4)	40 (38.0)	.30
Secretion obstruction	32 (31.4)	33 (31.4)	.99
Ventilatory failure	45 (44.1)	42 (40.0)	.57
Duration of mechanical ventilation, mean, days	4.5	5.2	.38
Risk factor for VAP			
Prior infection	23 (22.5)	30 (28.6)	.33
Prior antibiotic use	48 (47.0)	60 (57.1)	.16
Bronchodilator use	11 (10.8)	10 (9.5)	.82
Corticosteroid use	9 (8.8)	16 (15.2)	.2
Acid reduction agent use	75 (73.5)	69 (65.7)	.28
Reintubation	5 (4.9)	5 (4.8)	.99
Invasive device(s) present	59 (57.8)	65 (61.9)	.56
Nasogastric tube present	85 (83.3)	86 (81.9)	.99
Thoracoabdominal surgery	29 (28.4)	28 (26.7)	.87
APACHE II score, mean ± SD	16.7 ± 7.9	18.2 ± 8.1	.16

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; VAP, ventilator associated pneumonia.

TABLE 2. Outcomes for 207 Study Patients Who Received Mechanical Ventilation and Oral Decontamination

Variable	Chlorhexidine group (<i>n</i> = 102)	Normal saline group (<i>n</i> = 105)	<i>P</i>
No. (%) of patients who developed VAP	5 (4.9)	12 (11.4)	.08 ^a
No. of cases of VAP per 1,000 ventilator-days, mean	7	21	.04
No. (%) of patients with irritation of oral mucosa	10 (9.8)	1 (0.9)	.001

NOTE. VAP, ventilator-associated pneumonia.

^a Relative risk, 0.43 (95% confidence interval, 0.16-1.17).

stratified randomization according to the sex and hospital location of the eligible patient. Patients in the chlorhexidine group received oral care 4 times per day that involved brushing the teeth, suctioning any oral secretions, and rubbing the oropharyngeal mucosa with 15 mL of a 2% chlorhexidine solution formulated and produced by the hospital's pharmacy department. The patients in the normal saline group underwent the same oral care procedure, except that their procedures used normal saline solution instead of chlorhexidine solution. The oropharyngeal cleaning with 2% chlorhexidine solution or normal saline solution was continued until the endotracheal tube was removed. All participating wards employed their usual care protocols, according to which a semirecumbent body position was maintained, if possible. Neither selective decontamination of the digestive tract nor continuous aspiration of subglottic secretions were performed for any patient.

Each patient was examined daily for the presence of pneumonia. A diagnosis of VAP was made if the patient had a new, persistent, or progressive infiltrate visible on a chest radiograph in combination with at least 3 of the following 4 criteria: (1) body temperature greater than 38°C or less than 35.5°C, (2) leukocytosis (defined as more than 10×10^3 leukocytes/mm³) or leukopenia (defined as less than 3×10^3 leukocytes/mm³), (3) purulent tracheal aspirate, and/or (4) a semiquantitative culture of tracheal aspirate samples that was positive for pathogenic bacteria. An oropharyngeal swab sample was taken from each patient immediately after endotracheal intubation, on day 3 after intubation, on day 7 after intubation, and every 7 days thereafter until the endotracheal tube was removed or the patient developed pneumonia. The oropharyngeal swab sample was placed on blood agar and McConkey agar for semiquantitative culture. The bacterial colonies on agar plates were graded as 1+, 2+, 3+, or 4+ to indicate growth seen in quadrants 1, 2, 3, or 4 of the plates; the plates without growth were graded "no growth."

A sample size of 108 patients per group was estimated to be necessary in order to determine whether oral decontamination with 2% chlorhexidine solution could reduce the rate

of VAP from 14 to 7 episodes per 1,000 ventilator-days with 5% type I error (1-sided) and 80% power. The data were analyzed by descriptive statistics, the unpaired Student *t* test, χ^2 square statistics, and the Mann-Whitney *U* test, as appropriate. A *P* value of .05 or less was considered statistically significant.

Meta-analysis

Randomized controlled trials that used a 2% chlorhexidine formulation for oral decontamination as the sole intervention for patients receiving mechanical ventilation and reported the incidence of pneumonia as a study outcome were selected from the studies included in 3 recent meta-analyses.¹⁹⁻²¹ The details of the selected studies were reviewed, and the data were combined with the data from the present randomized controlled trial by use of RevMan software, version 4.2 (Cochrane Collaboration). The pooled effect sizes of relative risk were estimated with the Mantel-Haenszel fixed effect model.

RESULTS

Randomized Controlled Trial

Of 207 patients enrolled to the study, 102 were randomized to the chlorhexidine group and 105 to the normal saline group. Patients' demographic characteristics, location, disease severity, and duration of mechanical ventilation did not differ significantly (Table 1). The effectiveness and safety of using a 2% chlorhexidine solution for oral decontamination to prevent VAP are shown in Table 2. The incidence of VAP was 4.9% (5 of 102) in the chlorhexidine group and 11.4% (12 of 105) in the normal saline group (RR, 0.43 [95% CI 0.16-1.17]; *P* = .08). The mean number of cases of VAP was 7 episodes per 1,000 ventilator-days in the chlorhexidine group and 21 episodes per 1,000 ventilator-days in the normal saline group (*P* = .04). In all patients, VAP was caused by gram-negative bacilli. Mild and reversible irritation of the oral mucosa was observed in 10 (9.8%) of the chlorhexidine group, compared with 1 (0.9%) of the normal saline group (*P* = .001). The outcomes for 110 patients who received mechanical ventilation for longer than 2 days are shown in Table 3. The patients in the chlorhexidine group also had less risk of developing VAP, compared with the normal saline group.

TABLE 3. Outcomes for 110 Patients Who Received Mechanical Ventilation for More Than 2 Days

Variable	Chlorhexidine group (<i>n</i> = 58)	Normal saline group (<i>n</i> = 52)	<i>P</i>
No. (%) of patients who developed VAP	5 (8.6)	10 (19.2)	.11 ^a
No. of cases of VAP per 1,000 ventilator-days, mean	13	23	.06

NOTE. VAP, ventilator-associated pneumonia.

^a Relative risk, 0.45 (95% confidence interval, 0.16-1.23).

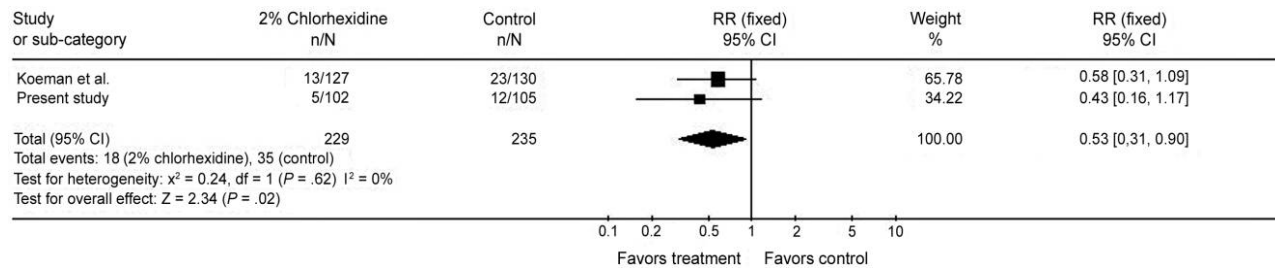


FIGURE. Forest plot of the meta-analysis (fixed effect model) of data from the Koeman et al.²² study and data from the present study on all patients who received mechanical ventilation. CI, confidence interval.

Observations regarding oropharyngeal colonization with gram-negative bacilli revealed the following findings: (1) gram-negative bacilli were present on the day of enrollment in 63 (61.8%) of the chlorhexidine group and in 71 (67.6%) of the normal saline group, (2) a total of 15 (38.5%) of 39 patients in the chlorhexidine group and 28 (82.4%) of 34 in the normal saline group were newly colonized with gram-negative bacilli, (3) a total of 12 (19.1%) of 63 patients in the chlorhexidine group and 0% of the normal saline group converted from being colonized with gram-negative bacilli to not being colonized, (4) a total of 21 (53.8%) of 39 patients in the chlorhexidine group and 3 (8.8%) of 34 in the normal saline group had no gram-negative bacilli recovered from oropharyngeal swab samples over the whole study period, (5) the amount of gram-negative bacilli recovered on culture increased in 9 (14.3%) of 63 patients in the chlorhexidine group and 36 (50.7%) of 71 in the normal saline group; and (6) the amount of gram-negative bacilli recovered was reduced in 27 (42.8%) of 63 patients in the chlorhexidine group and in 10 (14.1%) of 71 in the normal saline group. The overall mortality rate for the patients in the chlorhexidine group was 32.3% (36 of 102), compared with 35.2% (37 of 105) in the normal saline group ($P = .7$).

Meta-analysis

We found that there was only 1 randomized controlled trial that evaluated oral decontamination with a 2% chlorhexidine formulation as the sole intervention for patients who received mechanical ventilation that also reported the incidence of pneumonia as a study outcome.²² We performed a pooled analysis of data from that trial and data from all patients in the present trial, as well as a pooled analysis of data from that trial and data from the patients in the present trial who received mechanical ventilation for more than 48 hours. The results of the first pooled analysis are shown in the Figure. Heterogeneity was not detected in either analysis ($P > .5$). There was a significant reduction in the rate of VAP among patients in the chlorhexidine group, with a relative risk of 0.53 (95% CI, 0.31-0.90; $P = .02$) for all patients and a relative risk of 0.54 (95% CI, 0.31-0.92; $P = .02$) for patients who received mechanical ventilation for more than 48 hours. A total of 14 patients would need to receive oral decontam-

ination with 2% chlorhexidine solution to prevent 1 additional case of VAP.

DISCUSSION

Chlorhexidine is a broad spectrum antiseptic agent. Its spectrum of antimicrobial activity includes gram-negative and gram-positive bacteria.²³ Among its most important attributes is its persistence: it remains chemically active on tissue for up to 6 hours. Chlorhexidine solution has been used as an anti-infective oral rinse in dental medicine. Although oral decontamination with low concentrations of chlorhexidine (0.12%-0.2%) has been found to be effective in preventing pneumonia in patients undergoing cardiothoracic surgery, its role in preventing pneumonia in critically ill patients who received mechanical ventilation had not been established prior to 2006.¹⁹⁻²¹ Therefore, we hypothesized that oral decontamination with a higher concentration of chlorhexidine might be more effective at preventing pneumonia in critically ill patients than is decontamination with a low-concentration solution. We asked the hospital's pharmacy department to formulate and produce a 2% chlorhexidine oral solution. An in vitro study of locally produced 2% chlorhexidine solution in our laboratory revealed that it was active against multi-drug-resistant bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus*.

We were unable to do a blind study because the odor and taste of the chlorhexidine solution were quite different from those of the normal saline solution. However, the assessors who determined whether a patient developed pneumonia were unaware of the patient's study group assignment. The results of our randomized controlled trial demonstrated that oral decontamination with 2% chlorhexidine solution was effective at preventing pneumonia in patients who received mechanical ventilation, similar to the results of a recent study published in 2006.²² Our study paid more attention to oropharyngeal colonization with gram-negative bacilli, because more than 90% of cases of VAP in our hospital were caused by gram-negative bacilli.⁵ More than 60% of the patients in our study had oropharyngeal colonization with gram-negative bacilli, because a large proportion of them had chronic un-

derlying diseases or had been hospitalized prior to endotracheal intubation. Among the patients who received 2% chlorhexidine oral rinse, the rate of oropharyngeal colonization with gram-negative bacilli was reduced or the onset of colonization was delayed.

Although a combination of chlorhexidine and colistin resulted in better oropharyngeal decontamination for gram-negative bacteria than did chlorhexidine alone, both regimens appeared equally effective at preventing VAP.²² Therefore, use of 2% chlorhexidine solution alone should be sufficient for prevention of VAP in patients who receive mechanical ventilation. It should be noted that 9.8% of the patients who received 2% chlorhexidine oral solution developed irritation of the oral mucosa. We observed that many patients who developed irritation were hospitalized in wards in which the personnel responsible for oral care usually vigorously rubbed the oropharyngeal mucosa with gauze soaked with 2% chlorhexidine solution. The incidence of irritation was reduced after personnel were instructed to clean the oropharyngeal mucosa gently. Healthcare workers should be aware of this side effect and should discontinue the use of 2% chlorhexidine oral solution if a patient experiences severe irritation of the oral mucosa.

We analyzed combined data from our study and another study because both studies were randomized controlled trials and both used the same concentration of chlorhexidine. Although there were several differences between the studies with respect to the formulation of 2% chlorhexidine solution and the eligibility criteria of the patients enrolled, the test of heterogeneity revealed a *P* value of greater than 0.1, indicating that there was no significant heterogeneity between the studies and that the results from both studies could be combined. Similar to the results from other meta-analyses, the pooled analysis of data from the other trial and data from all patients from our study revealed a significant reduction in the rate of VAP in the chlorhexidine group, as did a pooled analysis of data from the other study and data for patients in this study who received more than 48 hours of mechanical ventilation.²⁰

Although oral decontamination with chlorhexidine reduced the risk of VAP in patients who received mechanical ventilation, no differences in duration of mechanical ventilation, length of intensive care unit stay, or mortality could be demonstrated.^{20,22} Our study also failed to demonstrate a reduction in the mortality rate among patients who received oral decontamination with chlorhexidine. Nevertheless, oral decontamination with 2% chlorhexidine solution for the prevention of VAP is still considered a cost-effective strategy, because the cost of the solution in Siriraj Hospital was only 40 cents per day and the number needed to treat is 14. At our institution, the mean total cost of 2% chlorhexidine solution for 14 patients was \$34, which is much less than the mean cost of antibiotic therapy to treat an episode of VAP (\$400). Therefore, beginning in August 2007, Siriraj Hospital adopted a policy that recommended oral decontamination

with 2% chlorhexidine solution for prevention of VAP for adult patients who receive mechanical ventilation.

ACKNOWLEDGMENTS

We thank Ms. Tanita Thaweethamcharoen for formulating and producing the 2% chlorhexidine oral solution, Ms. Suwanna Trakulsomboon for testing the antibacterial activity of the 2% chlorhexidine solution, the personnel in the laboratory of Division of Infectious Diseases and Tropical Medicine for performing cultures of oropharyngeal samples, Ms. Laksamee Watanamongkolsilp for data management, Ms. Chulaluk Komoltri for analyzing the data, Ms. Sunee Tanakumtorn for coordinating the study, Dr. Akarin Nimmannit for performing the meta-analysis, and Dr. Chairat Permpikul and Dr. Puttipanee Vorrakitpokatorn for their supervision.

Financial support. The Thailand Research Fund and Faculty of Medicine Siriraj Hospital.

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

Address reprint requests to Visanu Thamlikitkul MD, Professor of Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand (sivth@mahidol.ac.th).

REFERENCES

1. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) Study: EPIC International Advisory Committee. *JAMA* 1995; 274:639-644.
2. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med* 1999; 27:887-892.
3. Centers for Disease Control and Prevention. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004; 32:470-485.
4. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005; 33:2184-2193.
5. Danchaivijitr S, Dhiraputra C, Santiprasitkul S, Judaeng T. Prevalence and impacts of nosocomial infection in Thailand 2001. *J Med Assoc Thai* 2005; 88(suppl 10):S1-S9.
6. Garrouste-Orgeas M, Chevret S, Arlet G, et al. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients: a prospective study based on genomic DNA analysis. *Am J Respir Crit Care Med* 1997; 156:1647-1655.
7. Garcia R. A review of the possible role of oral and dental colonization on the occurrence of health care-associated pneumonia: underappreciated risk and a call for interventions. *Am J Infect Control* 2005; 33:527-541.
8. Bergmans DC, Bonten MJ, Gaillard CA, et al. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2001; 164:382-388.
9. Kollef M, Pittet D, Sanchez Garcia M, et al. A randomized double-blind trial of iseganan in prevention of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2006; 173:91-97.
10. Laggner AN, Tryba M, Georgopoulos A, et al. Oropharyngeal decontamination with gentamicin for long-term ventilated patients on stress ulcer prophylaxis with sucralfate? *Wien Klin Wochenschr* 1994; 106:15-19.
11. Rios F, Maskin B, Sanz VA. Prevention of ventilator associated pneumonia by oral decontamination: prospective, randomized, double-blind, placebo controlled study. In: Program and abstracts of the American Thoracic Society International Conference (San Diego). 2005. C95. Poster 608.
12. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlor-

- hexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. *Chest* 1996; 109:1556-1561.
13. Fourrier F, Cau-Pottier E, Boutigny H, Roussel-Delvallez M, Jourdain M, Chopin C. Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. *Intensive Care Med* 2000; 26:1239-1247.
 14. Fourrier F, Dubois D, Pronnier P, et al. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. *Crit Care Med* 2005; 33:1728-1735.
 15. MacNaughton PD, Bailey J, Donlin N, Branfield P, Williams A, Rowswell H. A randomised controlled trial assessing the efficacy of oral chlorhexidine in ventilated patients. European Society of Intensive Care Medicine, 17th Annual Congress, Berlin, Germany. *Intensive Care Med* 2004; 30(suppl):S5-S18.
 16. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. *Am J Crit Care* 2002; 11:567-570.
 17. Grap MJ, Munro CL, Elswick RK Jr, Sessler CN, Ward KR. Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: a pilot study. *Heart Lung* 2004; 33:83-91.
 18. *Guideline for the Prevention of Healthcare-Associated Pneumonia, 2004*. Atlanta, GA: Centers for Disease Control and Prevention, Healthcare Infection Control Practices Advisory Committee; 2004.
 19. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. *Crit Care Med* 2007; 35: 595-602.
 20. Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. *BMJ* 2007; 334:889-899.
 21. Kola A, Gastmeier P. Efficacy of oral chlorhexidine in preventing lower respiratory tract infections: meta-analysis of randomized controlled trials. *J Hosp Infect* 2007; 66:207-216.
 22. Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2006; 173:1348-1355.
 23. Denton GW. Chlorhexidine. In: Block SS, ed. *Disinfection, Sterilization, and Preservation*. 4th ed. Philadelphia, PA: Lea and Febiger; 1991.