Topical chlorhexidine for prevention of ventilator-associated pneumonia: A meta-analysis*

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Objective: **To assess the efficacy of topical chlorhexidine for prevention of ventilator-associated pneumonia (VAP) in a meta-analysis.**

Data Source: **Computerized PubMed and MEDLINE search supplemented by manual searches for relevant articles.**

Study Selection: **Randomized controlled trials evaluating efficacy of topical chlorhexidine applied to the oropharynx vs. placebo or standard care for prevention of VAP.**

Data Extraction: **Data were extracted on patient population, inclusion and exclusion criteria, diagnostic criteria for VAP, form and concentration of topical chlorhexidine used, incidence of VAP, and overall mortality.**

Data Synthesis: **Data on incidence of VAP and mortality were abstracted as dichotomous variables. Pooled estimates of the relative risk and 95% confidence intervals were obtained using the DerSimonian and Laird random effects model and the Mantel-Haenszel fixed effects model. Heterogeneity was assessed using the Cochran Q statistic and I^2. Subgroup analyses were used to explore heterogeneity.**

Results: **Seven randomized controlled trials met the inclusion criteria. Topical chlorhexidine resulted in a reduced incidence of VAP (relative risk, 0.74; 95% confidence interval, 0.56–0.96; $p = .02$) using a fixed effects model. Using the more conservative random effects model, the point estimate was similar (relative risk, 0.70; 95% confidence interval, 0.47–1.04; $p = .07$), but the results failed to achieve statistical significance. The I^2 test showed moderate heterogeneity. Subgroup analysis showed that the benefit of chlorhexidine was most marked in cardiac surgery patients (relative risk, 0.41; 95% confidence interval, 0.17–0.98; $p = .04$). There was no mortality benefit with chlorhexidine although the sample size was small.**

Conclusions: **Our analysis showed that topical chlorhexidine is beneficial in preventing VAP; the benefit is most marked in cardiac surgery patients. A large randomized trial is needed to determine the impact of topical chlorhexidine on mortality. (Crit Care Med 2007; 35:595–602)**

KEY WORDS: chlorhexidine; ventilator-associated pneumonia; nosocomial infection; critical care

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in the intensive care unit (ICU) (1); between 10% and 20% of patients receiving >48 hrs of mechanical ventilation will develop VAP (1, 2). VAP is associated with prolonged hospital stay (3–5), increased cost (6), and a two-fold excess risk of mortality (2).

Prevention of VAP is essential. Numerous studies have shown that for most endemic VAPs, the most important mechanism of infection is aspiration of oropharyngeal organisms into the distal bronchi, followed by bacterial proliferation and parenchymal invasion (7–9). Inflammation of the bronchiole wall involves the alveolar septi and air spaces leading to bronchopneumonia. The normal flora of the oropharynx in the nonintubated patient without critical illness is composed predominantly of viridans streptococci, *Haemophilus* species, and anaerobes. Salivary flow and content (immunoglobulin, fibronectin) are the major host factors maintaining the normal flora of the mouth (and dental plaque). Aerobic Gram-negative bacilli are rarely recovered from the oral secretions of healthy patients (10). However, during critical illness, especially in ICU patients, the oral flora shifts dramatically to a predominance of aerobic Gram-negative bacilli and *Staphylococcus aureus* (11).

Understanding this sequence of pathophysiologic events, it would seem logical that reducing concentrations of oral pathogenic microorganisms should have a beneficial effect for prevention of VAP. Selective digestive decontamination using antibiotics has been shown to be effective in preventing VAP (12–14); however, concern regarding the risk of emergence of antibiotic-resistant microorganisms has dampened enthusiasm for this approach (15).

More recently, topical application of an antiseptic, chlorhexidine, to the oral mucosa for prevention of VAP has been studied in randomized, controlled trials, which have reported mixed results: some showed little effect on the prevention of VAP (16), whereas others found a reduction in the incidence of VAP (17, 18). None of these trials was adequately powered to demonstrate potential benefits in other important outcome measures related to VAP such as ICU or hospital length of stay, duration of mechanical ventilation, and mortality. Recent review articles focusing on methods of preventing VAP have concluded that topical chlorhexidine for prevention of VAP is a promising but unproven method (19, 20). We undertook a meta-analysis to system-

***See also p. 668.**

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Supported, in part, by a 2006 Vision Grant from the Society of Critical Care Medicine (NS).

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/01.CCM.0000253395.70708.AC

atically review the published randomized clinical trials evaluating the use of topical chlorhexidine for prevention of VAP.

METHODS

We performed a computerized search of PubMed (including MEDLINE), Current Contents, CINAHL, DARE, and the Cochrane Network from inception until April 15, 2006, using the following keywords combined with chlorhexidine: *intensive care units, critical care, critical illness, ventilators, mechanical, respiratory tract infections, ventilator-associated pneumonia, pneumonia.* In addition we searched the following conference abstract databases: Conference Papers Index and BIOSIS RRM. Abstracts of meetings of the InterScience Conference on Antimicrobial Agents and Chemotherapy, the Infectious Diseases Society of America, and European Society of Intensive Care Medicine (1998–2005) were also reviewed.

We repeated the search with the same keywords using Google search engine (http://www.google.com). We reviewed National Institutes of Health Web site listings of ongoing trials (http://www.clinicaltrials.gov) and contacted authorities in the field for identification of additional unpublished studies. Reference lists of articles were searched to identify additional articles. No language restrictions were placed on the search.

Articles were included in our review if they met the following criteria: randomized controlled trials that compared topical oropharyngeal chlorhexidine with placebo or standard care and reported VAP as an outcome. We excluded case reports, review articles, letters, and editorials.

Both authors independently reviewed each report identified by the search strategy. Disagreements among abstracters regarding values or analysis assignments were resolved by discussion.

The Quality of Reporting of Meta-Analyses (QUOROM) checklist was followed for study selection, data abstraction, data synthesis, and reporting of results (21).

Data Abstraction and Statistical Analysis. Data were extracted using a standard form for each relevant study and included the total number of patients in the study, those randomized to chlorhexidine and the comparator, details regarding the randomization scheme, concentration and method of application of chlorhexidine, patient population, duration of mechanical ventilation, adverse effects of chlorhexidine, assessment of resistance to chlorhexidine, method of diagnosis, and incidence of VAP. Data on mortality and length of ICU stay were also extracted.

Data on incidence of ventilator-associated pneumonia and mortality were abstracted as dichotomous variables. We used the patient as the unit of analysis for the incidence of VAP and mortality. Other outcomes of interest were the incidence rate of VAP (reported as cases per 1000 mechanically ventilated patient-days), ICU length of stay, hospital length of stay, duration of mechanical ventilation, and the time from intubation to VAP occurrence. Whenever necessary, authors of included articles were contacted to obtain additional information required for the statistical analysis. In all situations, we used the bacteriologic diagnosis made by the authors as the etiology of the VAP. Colonization was defined as isolation of microorganisms without evidence of clinical infection.

Pooled estimates of the relative risk (RR) and 95% confidence intervals (CI) were obtained using the DerSimonian and Laird random effects model (22) and the Mantel-Haenszel fixed effects model (23). Heterogeneity was assessed using the Cochran Q statistic and I^2 ($100\% \times [Q - df]/Q$), where Q is Cochran's Q statistic and df is degrees of freedom (24). Degrees of freedom are equal to $k - 1$ where k is the number of studies. Negative values of I^2 are put equal to 0% so I^2 values can range between 0% and 100%. Zero percent indicates no observed heterogeneity; larger values indicate increasing heterogeneity. Subgroup analyses were used to explore the reasons for heterogeneity. Publication bias was assessed using a funnel plot and Eggers statistical test (25, 26). All statistical analyses were performed using Stats Direct Software (Cheshire, UK).

Sensitivity Analyses. We specified subgroup analyses *a priori*. One was to evaluate whether the effect of chlorhexidine differed by the patient population in which it was used. Thus, we performed analyses separately for cardiac surgery patients and all other patients. We also repeated the analyses including only the five published larger randomized controlled trials.

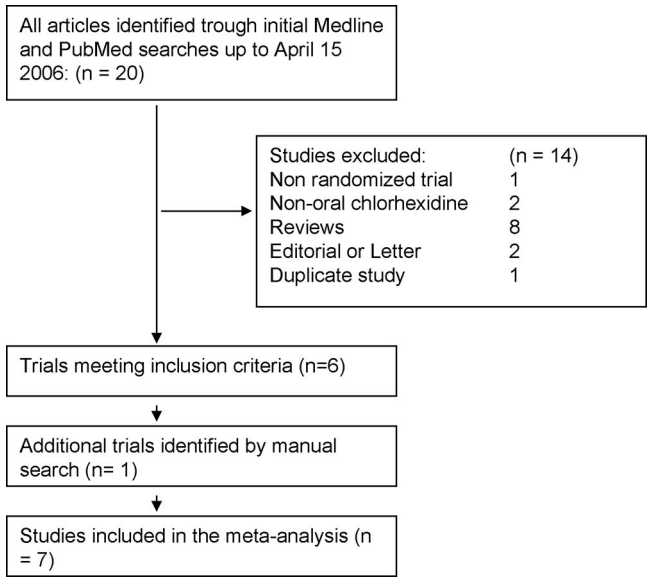

Figure 1. Literature search leading to selection of articles.

RESULTS

Study Selection. The database search retrieved 20 citations, of which six met our inclusion criteria (Fig. 1) (16–18, 27–29). Manual search identified one additional trial presented in abstract form (30). The remaining studies fell into one or more of the following exclusionary categories: nonrandomized trial (n = 1), nonoral chlorhexidine (n = 2), review article (n = 8), editorial or letter (n = 2), duplicate (n = 1).

All studies were in the English language. The interobserver agreement was high among the two data abstractors (κ score 0.80).

Study Characteristics. The seven trials enrolled 1,650 patients; 812 patients received a preparation of topical chlorhexidine applied to the oral mucosa and 838 patients received the comparator. Of the 838 patients not receiving chlorhexidine, 512 patients received placebo (16, 17, 29, 30); 35 patients received standard oral care (18, 28), and in one study (27), the control group (291 patients) received a phenolic oral rinse (Listerine). Two studies, conducted in cardiothoracic ICUs (17, 27), accounted for 55.4% of all the patients forming our population for the meta-analysis (443 in treatment groups and 471 as controls). The remaining five studies were conducted in medical or medical-surgical ICUs (16, 18, 28–30).

The study conducted by Koeman et al. (29) had three arms, and the arm using a combination of topical chlorhexidine and colistin (128 patients) was excluded from

Table 1. Characteristics of included studies

Author, Year (Ref. No.)	Setting and Inclusion Criteria	Exclusion Criteria	Definition of VAP	Time of Assessment of Mortality	Chlorhexidine Dosing Schedule	Comparator Agent
De Riso et al. 1996 (17)	Cardiothoracic ICU, open heart surgery	Death during surgery, preoperative infection or intubation, pregnancy, heart or lung transplant recipients, hypersensitivity to chlorhexidine	Clinical features. New or progressive pulmonary infiltrate, fever, leukocytosis, and purulent tracheobronchial secretions	In-hospital mortality	15 mL of 0.12% oropharyngeal rinse applied twice daily for 30 secs	Placebo
Houston et al. 2002 (27)	Cardiothoracic ICU, open heart surgery	Death during surgery, pregnancy, preoperative infection	Clinical features	Not specified	15 mL of 0.12% oropharyngeal rinse applied for 30 secs preoperatively and twice daily for 10 days postoperatively, or until extubation, tracheostomy, death, or diagnosis of pneumonia	Listerine
Fourrier et al. 2000 (18)	Medicosurgical ICU, >18 yrs old, anticipated stay in ICU 5 days, mechanical ventilation condition suggesting an ICU stay of 5 days	Edentulous patients	Temperature >38°C or <36°C, presence of infiltrates on chest radiography, leukocytosis or leukopenia, positive culture from tracheal aspirate (10^6 CFU/mL) and/or BAL (10^4 CFU/mL)	Not specified	0.2% gel three times daily	Mouth rinsing with isotonic sodium bicarbonate and oropharyngeal sterile aspiration four times daily
Fourrier et al. 2005 (16)	As above; in addition, only patients hospitalized for 48 hrs before admission to the ICU included	Edentulous patients and patients with tracheostomy tube before admission	As above	Number of deaths from day 0 to day 28	0.2% gel three times a day during the entire ICU stay, until day 28	Placebo
Koeman et al. 2006 (29)	Medical ICU; consecutive patients needing mechanical ventilation ≥48 hrs	Not mentioned	Not mentioned	Not specified	2% in white petrolatum vehicle, applied every 6 hrs by swabbing onto the buccal cavity	Placebo
MacNaughton et al. 2004 (30)	Medicosurgical ICU, consecutive patients needing mechanical ventilation ≥48 hrs	Treatment of infection on admission to ICU, chlorhexidine hypersensitivity	1. Leucocytosis 2. Fever >38°C 3. Deterioration in oxygenation/chest signs, new consolidation on chest radiograph 4. Significant bacterial growth on BAL 3 of 4 probable VAP 4 of 4 definite VAP	Data on both in-hospital and ICU mortality provided; in-hospital mortality used for statistical analysis	0.2% oral rinse twice daily	Placebo
Grap et al. 2004 (28)	All trauma victims and surgical patients >18 yrs old who required endotracheal intubation and mechanical ventilation	Edentulous patients	Clinical Pulmonary Infection Score >6	Mortality not an endpoint in this study	2 mL of 0.12% spray (20 sprays) or swab, single application in early postintubation period	Standard oral care

VAP, ventilator-associated pneumonia; ICU, intensive care unit; CFU, colony-forming units; BAL, bronchoalveolar lavage.

the analyses. The characteristics of the seven randomized controlled trials are summarized in Table 1. In the two trials conducted in cardiothoracic ICU patients (17, 27), the intervention was implemented before elective endotracheal intubation and continued until extubation, discharge from the ICU, or death; in the remainder it was continued until extubation (28–30) or for the entire ICU stay (16, 18).

In two trials (17, 27) the investigators used 15 mL of 0.12% chlorhexidine rinse that was applied to the buccal pharyngeal, gingival, tongue, and tooth surfaces for 30 secs twice daily (Table 1). Fourrier et al. (16, 18) used a 0.2% gel applied three times a day to the dental and gingival surfaces. MacNaughton et al. (30)

Table 2. The incidence of ventilator-associated pneumonia and mortality with chlorhexidine

Author, Year (Ref. No.)	No. of Patients		Mortality, No. (%)		Ventilator-Associated Pneumonia, No. (%)	
	Chlorhexidine	Comparator	Chlorhexidine	Comparator	Chlorhexidine	Comparator
DeRiso et al. 1996 (17)	173	180	2 (1.16)	10 (5.56)	3[a] (1.73)	9[a] (5.00)
Houston et al. 2002 (27)	270	291	6 (2.22)	3 (3.30)	4[a] (1.48)	9[a] (9.89)
Fourrier et al. 2000 (18)	30	30	3 (10)	7 (23.33)	5[a] (16.67)	15[a] (50.00)
Fourrier et al. 2005 (16)	114	114	31 (27.19)	24 (21.05)	13[b] (11.40)	12[b] (10.53)
Koeman et al. 2006 (29)	127	130	49 (38.58)	39 (30.00)	13[a] (10.24)	23[a] (17.69)
MacNaughton et al. 2004 (30)	91	88	36 (39.56)	33 (37.50)	32[a,c] (35.16)	28[a,c] (32.82)
Grap et al. 2004 (28)	7[d]	5[d]	NR	NR	4[a] (57.14)	3[a] (60.00)

NR, not reported.

[a]Number of patients with ventilator-associated pneumonia; [b]number of episodes of ventilator-associated pneumonia; [c]only definite pneumonia; [d]patients for whom data was available at 48 hrs.

also used a 0.2% oral rinse but the frequency of use was not specified. Koeman et al. (29) used a higher concentration of chlorhexidine 2.0% applied every 6 hrs to the buccal cavity, and Grap et al. (28) used a single oral application of 0.12% chlorhexidine spray or swab.

Selective digestive decontamination was not used or was not mentioned in the included trials. DeRiso et al. (17) used H2 blocking agents for stress ulcer prophylaxis. Only one trial explicitly reported that head of bed elevation to 30° was routinely done and that subglottic suctioning was not used (29). In the studies including cardiac surgery patients, patients received cefuroxime or vancomycin perioperatively (17, 27). In the remaining studies, a large proportion of patients in the ICU received systemic antibiotic treatment of varying type and duration.

Details of Randomization. Block randomization was used in two trials (16, 28); in another two randomization was achieved using a computer-generated balanced randomization table (18, 29) or computer-driven random number generator (17). Houston et al. (27) reported that patients were consecutively randomized according to the medical record numbers. Details of randomization were not provided in the study by MacNaughton et al (30).

Two studies were conducted in a double-blind manner (16, 29), in three, investigators and healthcare providers were not aware of the treatment given (18, 28, 30), and in one, investigators reported that double-blind design was used but no details were provided (17). Finally, it appears that in the study by Houston et al. (27), neither patients nor investigators were blinded to the treatment used.

Mortality data were reported in six trials.

Intention to treat analysis was performed in five trials (16–18, 27, 29).

Diagnosis of VAP. The authors used various definitions of VAP in their studies. The combination of clinical features and positive respiratory culture was used in four studies (16, 18, 29, 30) and clinical assessment alone in two studies (17, 27). Grap et al. (28) used Clinical Pulmonary Infection Score >6 to diagnose VAP.

One study (16) reported only the number of episodes of VAP and not the number of infected patients. We therefore used the number of VAPs for our analyses.

Effect of Chlorhexidine on Oral Flora. Five trials attempted to evaluate the impact of chlorhexidine on colonization of saliva, dental plaque, or endotracheal surfaces. Fourrier et al. (18) sampled dental plaque for bacterial cultures on days 0, 5–7, and 10–12 and every week. Nasal and tracheal aspirates were obtained on admission and every fifth day. The authors found that more dental plaque samples were colonized in the comparator group (27%) than the treatment group (13%, p not significant). However, after day 10, the frequency of dental plaque colonization was similar. The results of tracheal aspirate cultures during the intervention were not reported. In a more recent study by the same group of investigators, similar results were noted with regard to dental plaque bacterial colonization; 29% of cultures were positive in the treatment group compared with 37% in the placebo group in a subgroup of 66 patients who underwent sampling on days 0, 5, and 10 (16). Two studies did not report changes in oropharyngeal flora in their study (17, 30), and Houston et al. (27) used quantitative sputum bacterial cultures to assess respiratory tract colonization. In the study by Koeman et al. (29), oropharyngeal swabs were obtained daily and quantitatively analyzed for Gram-positive and Gram-negative microorganisms. Endotracheal colonization was monitored twice weekly and was reduced in the chlorhexidine group compared with placebo. Grap et al. (28) also found reduced oral colonization in the treatment group compared with placebo.

Incidence of VAP. Table 2 shows the incidence of VAP in the included trials. The incidence of VAP in the control groups of both studies conducted in cardiothoracic ICUs was markedly lower than in the trials conducted in general medicosurgical ICUs (18 of 471, 3.82% for both studies, compared with 22.07% in the remainder). In two trials, oropharyngeal chlorhexidine did not result in a reduced incidence of VAP (16, 30). In five trials, chlorhexidine was associated with a beneficial effect for prevention of VAP (17, 18, 27–29); in two trials, however, this decrease was not statistically significant (17, 27). The trial by DeRiso et al. (17) showed a significant decline in overall nosocomial infection rate, and the trial by Houston et al. (27) found a statistically significant reduction in VAP only in patients intubated for >24 hrs.

Overall, 9.11% (7 of 812) of patients developed VAP in the treatment group compared with 11.81% (99 of 838) of patients in the comparator group. The Mantel-Haenszel pooled estimate of relative risk was 0.74 (95% CI, 0.56–0.96; $p = .03$) (Fig. 2), indicating a beneficial effect with chlorhexidine for prevention of VAP. The Cochran Q statistic for heterogeneity was not significant ($p = .10$), but I^2 showed moderate heterogeneity. Using the random effects model, the DerSimonian-Laird pooled relative risk was 0.70 (95% CI, 0.48–1.04; $p = .08$) (Fig. 3); whereas the point estimate reflects a 30% relative risk reduction in VAP, the 95% CI includes 1. Only two studies reported the rate of VAP using patient-days as a denominator (16,

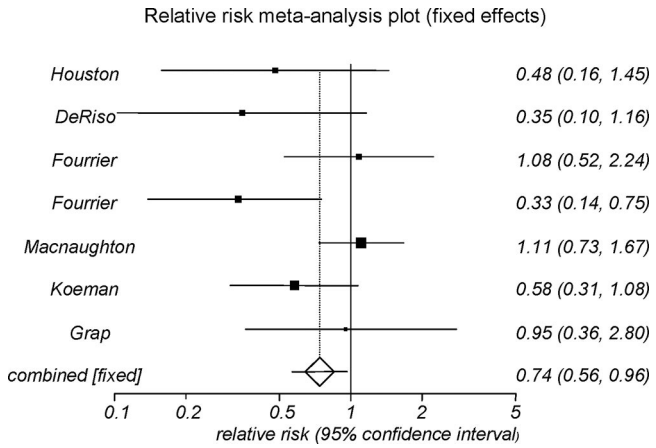

Figure 2. Relative risk of ventilator-associated pneumonia with chlorhexidine and comparator using a fixed effects model. The relative risk was 0.74 (95% confidence interval, 0.56, 0.96), indicating a 26% relative risk reduction in ventilator-associated pneumonia with the use of chlorhexidine.

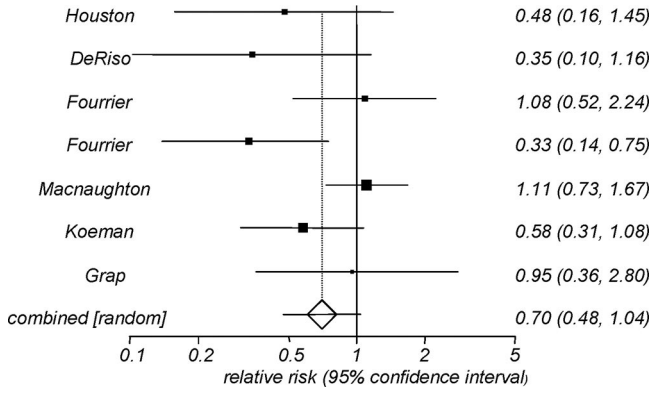

Figure 3. Relative risk of ventilator-associated pneumonia with chlorhexidine and comparator using a random effects model. The relative risk was 0.70 (95% confidence interval, 0.48, 1.04), indicating a 30% relative risk reduction in ventilator-associated pneumonia with the use of chlorhexidine. The results were not statistically significant.

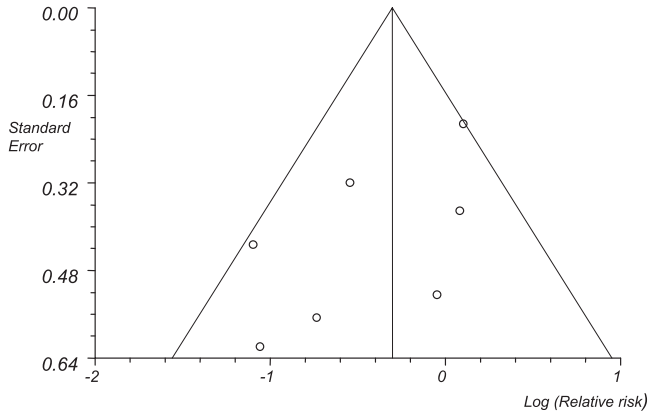

Figure 4. Assessment of publication bias using a funnel plot. The plot does not show publication bias.

18), and we were unable to calculate a combined rate ratio.

Publication Bias. Given the small number of studies that met our inclusion criteria, publication bias was of concern. Publication bias was assessed using a funnel plot and Eggers test (Fig. 4). The shape of the funnel plot was symmetrical, indicating no publication bias, and Eggers test was not statistically significant ($p = .10$).

Assessment of Heterogeneity. There was substantial clinical heterogeneity in the included studies, with differing patient populations, concentration, and frequency of application of chlorhexidine and definition of VAP. Using the Q statistic, we did not find statistical heterogeneity. However, an alternate test for heterogeneity, I^2, was 43%, indicating moderate heterogeneity.

Subgroup Analysis. To explore the reasons for the heterogeneity, we repeated the analysis limited to studies assessing the efficacy of chlorhexidine for prevention of VAP in cardiac surgery patients. We found that use of chlorhexidine was associated with a relative risk of 0.41 (95% CI, 0.17–0.98; $p = .04$), indicating a 59% relative risk reduction for VAP for that patient population. We also redid the analyses a) including only the five published randomized trials and b) excluding the study by Grap et al (28), because of its different diagnostic criteria for VAP. The efficacy of chlorhexidine in the five published randomized trials was RR, 0.57; 95% CI, 0.39–0.83 (fixed effects) and RR, 0.57; 95% CI, 0.37–0.87 (random effects model). Including the five published randomized trials and one study in abstract form but excluding Grap et al., we found that RR was 0.73; 95% CI, 0.55–0.96 (fixed effects) and RR, 0.66; 95% CI, 0.42–1.04 (random effects).

Mortality. Data on mortality were available for six of the seven included studies. Overall 15.64% (127 of 812) of patients died in the treatment group, and 13.84% (116 of 838) died in the comparator group (Table 2). The relative risk for mortality was 1.07 (95% CI, 0.76–1.51, $p = .69$), using the random effects model (Fig. 5), indicating no statistically significant beneficial effect of chlorhexidine on mortality; however, the number of patients was too small to adequately assess this important outcome.

Other Outcomes. Five studies evaluated other outcomes, such as ICU or hospital length of stay, duration of mechanical ventilation, and reintubation rate. Fourrier et al. (18) found a shorter length of stay in the ICU (24 ± 19 vs. 18 ± 16, p not significant) and shorter duration of mechanical ventilation in the treated group (18 ± 20 vs. 13 ± 12, p not significant), although the results were not statistically significant. Five other studies did not find any differences in duration of mechanical ventilation or ICU length of stay (16, 17, 27, 29, 30).

Cost of Chlorhexidine. Only three studies estimated the costs of chlorhexidine (17, 27, 29). Houston et al. (27) estimated that the yearly cost of using

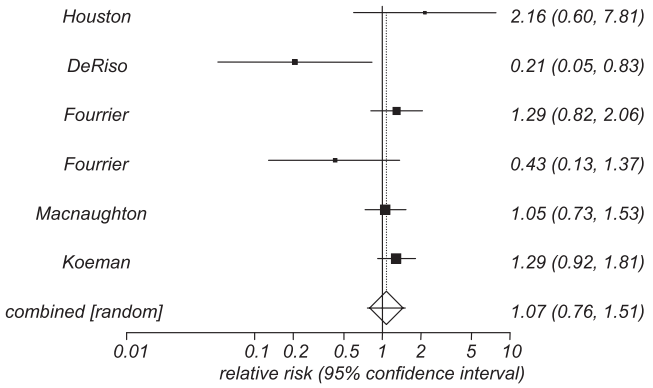

Figure 5. The impact of chlorhexidine on mortality. No statistically significant reduction in mortality was found.

chlorhexidine for all cardiac surgery patients was $700. DeRiso et al. (17) estimated $40,000 savings during their study due to reduction in antimicrobial use in the treatment group. Koeman et al. (29) calculated that 8 days of treatment with chlorhexidine (including nursing time, gloves, and cost of chlorhexidine) cost <$100. No formal cost-effectiveness analysis was undertaken in any study.

Resistance to Chlorhexidine. In six of the seven studies, investigators did not report data on resistance to chlorhexidine among bacterial isolates recovered from study patients. Only Grap et al. (28) mentioned that in one case application of chlorhexidine did not eliminate growth of *P. aeruginosa* on agar plates. However, they attributed it to a high colony count of organisms rather than to true resistance.

Adverse Effects of Chlorhexidine. Adverse effects of chlorhexidine, such as mouth dryness, staining of teeth, or unpleasant taste, were not reported in any of the included studies. This issue was not explicitly addressed, however, and it is possible that side effects of chlorhexidine were not observed, were not sought, or were so minor that investigators did not think that they were clinically significant.

DISCUSSION

Recent studies have found that aspiration of oropharyngeal flora in mechanically ventilated patients is a major mechanism of developing VAP. In a prospective cohort study in 57 ICU patients, Fourrier et al. (31) demonstrated an association between colonization of dental plaque by aerobic pathogens, which occurred in 46% of patients by day 10 of ICU stay, and subsequent development of nosocomial pneumonia. Emerging evidence has linked oral health to aspiration pneumonia in the elderly (32–34). Attention has therefore focused on whether improvement in oral hygiene may lead to a reduced incidence of VAP. Among the strategies that have been studied, application of chlorhexidine to the oropharyngeal mucosa has had promising results in some but not all clinical trials.

Our analysis combining the results of seven randomized controlled trials found that chlorhexidine is associated with a 30% relative reduction in the risk of VAP. Although the statistical significance was retained only in the fixed effects model and not in the random effects model, the point estimates were very similar for both analyses. The random effects model provides a more conservative estimate of the 95% confidence interval, taking heterogeneity into account. Exploring heterogeneity by subgroup analyses, we found that the beneficial effect of chlorhexidine was most apparent in the two trials that were limited to cardiac surgery patients (17, 27). Coronary artery bypass surgery is usually an elective procedure, patients deemed to be fit for such surgery are usually in better general health than those admitted to medical ICUs, and intubation is performed under optimal conditions by the anesthesiologist, all of which may influence baseline risk of VAP.

It is difficult to tell whether topical chlorhexidine is more effective for prevention of early rather than late VAP. In both studies by Fourrier et al. (16, 18), there was no difference between chlorhexidine and control groups in the time to development of nosocomial infection. On the other hand, topical chlorhexidine was effective in preventing VAP in patients who underwent cardiothoracic surgery and who were intubated only for a short period of time. It is likely that topical chlorohexidine may delay rather than prevent the development of VAP. Such delay in oropharyngeal colonization would mainly benefit patients who require only short period of ventilatory support (e.g., patients after open heart surgery). In critically ill medical patients who require prolonged period of ventilatory support, such delay would have only limited effect on overall incidence of VAP.

A large recent trial by Fourrier et al. (16) included in our analysis failed to find a benefit of chlorhexidine for prevention of VAP. The baseline characteristics and risk of nosocomial infections were significantly different for patients enrolled in this trial than in the other included studies. The mean Simplified Acute Physiology Score II on admission was 45, underscoring the fact that enrolled patients were critically ill. The majority of these patients underwent emergency intubation, and half of them were intubated before they were admitted to ICU.

The varying concentration of the chlorhexidine solutions used in the included studies may have affected the results of the trials. In the study by Koeman et al. (29), a 2% solution of chlorhexidine was used, a much higher concentration than in the other published studies, most of which used a 0.12% or 0.2% solution; this may partially explain the benefit of chlorhexidine for reducing VAP in this study.

The main limitation of our meta-analysis is the heterogeneity stemming from the design of the original studies. Differing patient populations, definitions of VAP, and concentration of chlorhexidine used contributed to the heterogeneity. We attempted to address this by undertaking subgroup analyses. In the subgroup analyses, chlorhexidine was most beneficial for prevention of VAP for cardiac surgery patients.

Adverse effects of the topical preparation of chlorhexidine were not explicitly addressed in the published clinical trials included in our meta-analysis. Reported adverse effects of oral use of chlorhexidine include staining of the teeth, which is reversible with professional cleaning (35), and a transient abnormality of taste (35, 36). Although in general, chlorhexidine topical preparations for prevention of VAP appear to be safe and well tolerated, future clinical trials using chlorhexidine should endeavor to document the presence or absence of adverse events.

In our analysis, no effect of chlorhexidine on reduction of mortality was found. None of the individual trials were powered to detect mortality differences, and it must be acknowledged that despite combining the studies, the sample size was inadequate to detect a survival advantage with chlorhexidine.

A potential concern with the prolonged use of antiseptic agents is the emergence of microbial resistance (37). Frequent exposure of the oropharyngeal flora to topically applied chlorhexidine may result in development of resistance to biocides. In clinical trials of chlorhexidine-impregnated vascular devices, resistance to chlorhexidine was not detected. In a recent well-designed trial comparing a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine to a standard uncoated catheter for prevention of intravascular device-related bacteremia, the investigators made a rigorous attempt to detect antiseptic resistance (38). They found that the zones of inhibition to chlorhexidine were similar for organisms recovered from antiseptic and control catheters. However, *in vitro* studies of *Pseudomonas stutzeri* exposed to slowly increasing concentrations of chlorhexidine found emergence of resistance to chlorhexidine and several classes of therapeutic antimicrobial agents (39). None of the published clinical trials included in our analysis adequately assessed emergence of resistance to chlorhexidine among isolates recovered from sputum or bronchoalveolar lavage. Serial cultures of oropharyngeal and lower respiratory specimens should be obtained, inoculated on selective media, and tested for susceptibility to chlorhexidine to determine an increase in minimum inhibitory concentration indicating resistance.

CONCLUSIONS

Topical application of chlorhexidine is useful for preventing VAP in mechanically ventilated patients. The optimal concentration, frequency of application, effect on promoting resistance among oropharyngeal flora, and cost-effectiveness of chlorhexidine should be addressed in future studies.

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