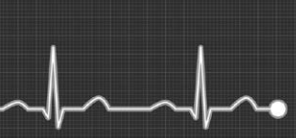

Review Article

Toothbrushing For Critically Ill Mechanically Ventilated Patients: A Systematic Review and Meta-Analysis of Randomized Trials Evaluating Ventilator-Associated Pneumonia*

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Background: Oral care may decrease ventilator-associated pneumonia in the ICU. The objective of this review was to summarize and critically appraise randomized trials in mechanically ventilated patients in the ICU testing the effect of oral care strategies involving toothbrushing on ventilator-associated pneumonia.

Search Methods: We searched EMBASE, MEDLINE, and the Cochrane Controlled Trials Register and Database of Systematic Reviews from 1980 until March 2012, independently and in duplicate, as well as personal files and reference lists. In duplicate, articles were selected if they were randomized trials, enrolled adult critically ill patients, compared any kind of oral care involving toothbrushing with any other kind of oral care or control with or without toothbrushing, and examined ventilator-associated pneumonia. In duplicate, we abstracted trial characteristics and quality using the Cochrane risk of bias tool. The results were combined using a random effects model.

Results: We included six trials enrolling 1,408 patients, five of which compared toothbrushing to usual oral care and one of which compared electric with manual toothbrushing. In four trials, there was a trend toward lower ventilator-associated pneumonia rates (risk ratio, 0.77; 95% confidence interval, 0.50–1.21; $p = 0.26$). This trend was also observed in one trial reporting fewer cases of ventilator-associated pneumonia per 1,000 ventilator days (20.68 vs. 25.89; $p = 0.53$) in patients receiving toothbrushing vs. no toothbrushing. The only trial with low risk of bias suggested that toothbrushing significantly reduced ventilator-associated pneumonia (risk ratio, 0.26; 95% confidence interval, 0.10–0.67; $p = 0.006$). Use of chlorhexidine antisepsis seems to attenuate the effect of toothbrushing on ventilator-associated pneumonia (p for the interaction = 0.02). One trial comparing electric vs. manual toothbrushing showed no difference in ventilator-associated pneumonia rates (risk ratio, 0.96; 95% confidence interval, 0.47–1.96; $p = 0.91$). Toothbrushing did not impact on length of ICU stay, or ICU or hospital mortality.

Conclusions: In intubated, mechanically ventilated critically ill patients, toothbrushing did not significantly reduce the risk of ventilator-associated pneumonia overall. Toothbrushing has no effect on mortality or length of stay. Electric and manual toothbrushing seem to have similar effects. More research is needed on this aspect of oral care to evaluate its potential to decrease ventilator-associated pneumonia. (*Crit Care Med* 2013; 41:646–655)

Key Words: critical illness; dental plaque; oral care; ventilator-associated pneumonia

***See also p. 691.**

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The authors have not disclosed any potential conflicts of interest.

There was no dedicated funding to support this systematic review. Dr. Cook is a Research Chair of the Canadian Institutes of Health Research.

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DOI: 10.1097/CCM.0b013e3182742d45

Ventilator-associated pneumonia (VAP) is among the commonest nosocomial infection in the ICU although the incidence may be decreasing, partly due to increased application of effective VAP prevention strategies (1). In some studies, VAP is associated with increased health care resource use and an increased risk of death (2, 3). The oropharynx and the upper gastrointestinal tract are the main reservoirs for pathogens associated with VAP (4, 5). Microaspiration of oral bacteria into the lung can result in VAP (6).

Critical illness and intubation interfere with host defenses, leading to mechanical injury, xerostomia, changes in dental plaque, oral flora, and oral immunity that increase the risk of pneumonia (5, 7, 8). Dental plaque and the oral mucosa can be

colonized with potential respiratory pathogens within a few days of intubation (9, 10). During intubation, microbes in the oral flora shift from predominantly Gram-positive organisms to Gram-negative species and yeast due to a loss of the protein fibropectin, a streptococcal binding site (7, 8, 11, 12). Furthermore, genetically identical pathogens have been isolated from the dental plaque and bronchoscopic cultures of mechanically ventilated patients suspected of pneumonia (13, 14). Baseline risk factors such as poor nutrition, dentition, and oral hygiene may potentiate oral bacterial overgrowth (15).

Oral care in the ICU is provided by nurses and deemed of moderate-to-high importance compared with other care activities (16–24). Most nurses use foam swabs or toothettes to clean the teeth and oral cavity (18, 21–25), and a minority report regular toothbrush use (16, 17, 19, 22, 23) although toothbrushes more effectively remove plaque than swabs (26).

Mechanical and pharmacologic strategies can reduce dental plaque load (5). Numerous randomized trials summarized in meta-analyses show that chlorhexidine can reduce VAP (27, 28). Observational studies of toothbrushing demonstrate improved oral health (29–31), reduced plaque load (31), less VAP (30, 32–35), and cost savings (34). The uptake of toothbrushing seems to be increasing over time, perhaps related to oral care quality improvement initiatives (29, 32, 33, 36), but randomized controlled trials have yielded conflicting results on the impact of toothbrushing on VAP (37–41).

The objective of this systematic review was to evaluate the effect of oral care using toothbrushing in mechanically ventilated critically ill adults as a strategy to reduce the occurrence of VAP.

METHODS

Trial Identification

We searched seven databases (EMBASE, MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, clinical trials.gov, and controlled-trials.com) for relevant trials from 1980 to April 2012. We reviewed personal files, reference lists of review articles, and eligible trials for additional trials. We also contacted companies that manufacture toothbrushes and toothpaste.

Eligibility Criteria

The inclusion criteria were as follows: 1) design: randomized controlled parallel group or factorial trial; 2) population: adult (18 years or older) mechanically ventilated critically ill patients; 3) intervention: any oral care strategy involving toothbrushing compared with any other strategy or control with or without toothbrushing; and 4) outcome: VAP.

Trials were excluded if they were pseudorandomized, published in abstract form only, or if they focused only on oral care using antiseptic strategies (e.g., chlorhexidine) or antibiotic strategies (e.g., any component of selective digestive decontamination). We had no language restrictions.

Trial Selection

We selected articles for this review in duplicate by examining titles, abstracts, and the full text if a potentially relevant trial was identified. We translated non-English reports to English as necessary.

Data Abstraction

In duplicate and independently, two reviewers abstracted data on the design, patient population, intervention and comparison, and clinical outcomes. The primary outcome of interest was VAP. Other outcomes of interest were length of ICU stay and ICU and hospital mortality.

Risk of Bias Assessment

In duplicate and independently, two reviewers assessed trial methodologic quality using the risk of bias tool recommended by the Cochrane Collaboration. For each trial, the risk of bias was reported as "low risk," "unclear risk," or "high risk" in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (42). For each outcome, we independently rated in duplicate the overall quality of evidence (confidence in effect estimates) using the GRADE approach in which trials begin as high-quality evidence, but may be rated down by one or more of five categories of limitations: risk of bias, inconsistency, indirectness, imprecision, and reporting bias (43). Finally, the overall risk of bias for an individual trial was categorized as "low" (if the risk of bias was low in all domains), "unclear" (if the risk of bias was unclear in at least one domain, with no high risk of bias domains), or "high" (if the risk of bias was high in one or more domains). Disagreement was resolved by discussion and consensus. We attempted to contact the authors and requested any necessary information not contained in publications.

Data Synthesis

We combined trial data to estimate the pooled risk ratio (RR) and 95% confidence intervals (CIs). Pooled RRs were calculated using the Mantel-Haenszel estimator. We calculated mean differences for length of stay. The random effects model of

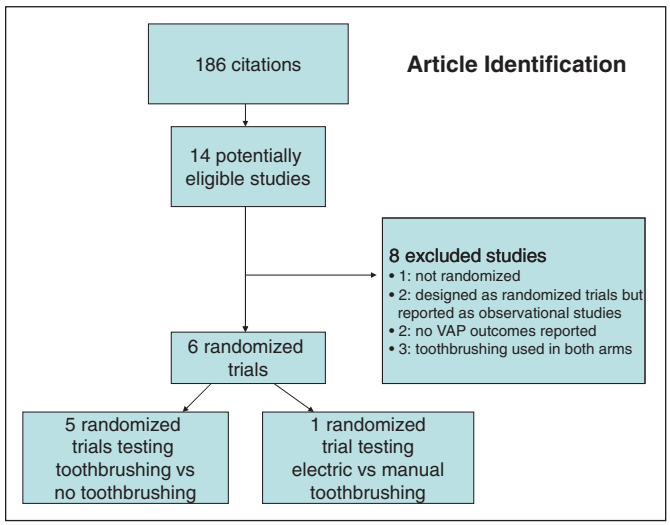

Figure 1. Article identification.

TABLE 1. Randomized Studies Evaluating the Effect of Toothbrushing on the Prevention of VAP

Trial (Sample Size)	Population	Intervention	Cointerventions	Pneumonia Definition	Outcome
Lorente ($n = 436$)	Intubated patients in medical, surgical, and trauma ICUs, and mechanically ventilated >24 hrs. Mean age: 61 yrs; mean APACHE II: 18.5.	*Intervention*: 1. Endotracheal cuff pressure tested 2. Oropharyngeal secretions aspirated 3. Gauze impregnated with 20 mL of 0.12% chlorhexidine used to cleanse the teeth, tongue, and muscosal surfaces 4. Oral cavity injection of 10 mL of 0.12% chlorhexidine 5. Oropharyngeal aspirations aspirated after 30 s 6. Manual brushing with a brush impregnated with 0.12% chlorhexidine Procedure completed three times daily by nurses *Control*: 1. Endotracheal cuff pressure tested 2. Oropharyngeal secretions aspirated 3. Gauze impregnated with 20 mL of 0.12% chlorhexidine used to cleanse the teeth, tongue, and mucosal surfaces 4. Oral cavity injection of 10 mL of 0.12% chlorhexidine 5. Oropharyngeal aspirations aspirated after 30 s Procedure completed three times daily by nurses	Well described and all equal	All the following criteria to be fulfilled: 1. New onset purulent bronchial sputum 2. Temperature $> 38°C$ or $< 35.5°C$; 3. WBC > 10 or < 4; 4. CXR showing new or progressive infiltrates;e) tracheal aspirate quantitative cultures $> 10^6$ CFU/mL	VAP Mortality Antibiotic-free days Ventilator-free days ICU length of stay
Prendergast ($n = 78$)	Neuro ICU patients and intubated within 24 hrs of admission. Mean age: 53 yrs	*Intervention*: 1. Tongue scraping 2. Toothbrushing with an electric toothbrush and non-foaming toothpaste for 2 mins 3. Moisturizing agent to oral mucosa and lips Procedure completed two times daily by nurses *Standard oral care:* 1. Toothbrushing with a manual, pediatric toothbrush and nonfoaming toothpaste for 2 mins 2. Moisturizing agent to oral mucosa and lips Procedure completed two times daily by nurses	Described but not equal or not sure	VAP was defined with documentation of a new or progressive pulmonary infiltrate together with two or three of the following: fever, leukocytosis, or purulent tracheobronchial secretions as per CDC	Oral colonization Respiratory colonization VAP
Biosca ($n = 147$)	Adult medical, surgical, or trauma patients in the ICU; mechanically ventilated > 48 hrs. Mean age: 54 yrs.	*Intervention (Raspall)*: 1. Wash hands 2. Elevate head of the bed 30–45° 3. Inform patient of the procedure 4. Measure and adjust cuff pressure to 25–30 cm H_2O 5. Clean teeth, tongue, and mouth with a swab impregnated with 0.12% chlorhexidine digluconate 6. Apply 10 mL of 0.12% chlorhexidine digluconate 7. Leave on for 30 s, then aspirate excess solution 8. Toothbrushing for 2 mins (Braun Oral B-Advance Power 450 TX), brushing buccal surfaces, palate and teeth clockwise from the gums to the incisors Procedure completed two times daily by nurses *Control (Standard)*: 1. Wash hands 2. Elevate head of the bed 30–45° 3. Inform patient of the procedure 4. Aspirate oropharyngeal secretions 5. Measure and adjust cuff pressure to 25–30 cm H_2O 6. Clean teeth, tongue, and mouth with swab impregnated with 0.12% chlorhexidine digluconate 7. Apply 10 mL of 0.12% chlorhexidine digluconate 8. Leave for 30 s, then aspirate excess solution Procedure completed two times daily by nurses	Not clear	VAP was identified according to clinical, medical, and microbiological criteria	VAP Plaque index score Colonization patterns
Yao ($n = 53$)	Adult, intubated mechanically ventilated postoperative neurosurgical patients admitted to a surgical ICU;	All patients received usual care including daily oral care with toothette oral or cotton swabs *Intervention*: 1. Elevate head of bed 30–45°, and suction hypopharyngeal secretions	Not described	VAP was defined as a modified CPIS > 6; modified CPIS is based on seven items, including temperature	Oral health and hygiene (OAG scores and the plaque index) VAP

(Continued)

TABLE 1. (*Continued*). Randomized Studies Evaluating the Effect of Toothbrushing on the Prevention of VAP

Trial (Sample Size)	Population	Intervention	Cointerventions	Pneumonia Definition	Outcome
	expected length of ICU stay > 2 d; and expected duration of mechanical ventilation > 48 hrs. Mean age: 60 yrs; mean APACHE II: 19.5.	2. Moisturize oral cavity with 5–10 mL purified water 3. Clean teeth with an electric toothbrush and clean lingual sides with a soft pediatric toothbrush 4. Tongue, gums, and mucosa massaged using a soft pediatric toothbrush 5. Oral cavity cleaned using a toothette swab connected to a suction tube and rinsed with 50 mL purified water 6. Hypopharyngeal suctioning Procedure completed two times daily by trained intervention nurse *Control*: 1. Elevate head of bed 30–45°, and suction hypopharyngeal secretions 2. Moisturize lips with a toothette swab with purified water 3. Hypopharyngeal suctioning Procedure completed two times daily by trained intervention nurse		WBCs, tracheal secretions, oxygenation, CXR results (no infiltration/diffused infiltration/localized infiltration, interpreted by a board-certified pulmonologist, blinded to group assignment), progression of pulmonary infiltrate (yes/no, interpreted by the same pulmonologist), and tracheal aspirate culture (total CPIS scores can range from 0 to 14)	
Pobo ($n = 147$)	Adult medical, surgical, and trauma ICU patients; mechanically ventilated > 12 hrs; and expected to be ventilated > 48 hrs. Mean age: 54 yrs; mean APACHE II: 18.8.	*Intervention*: 1. Head of bed elevated at 30° 2. Aspiration of oropharyngeal secretions 3. Adjustment of endotracheal cuff pressure 4. Gauze containing 20 mL of 0.12% chlorhexidine applied to all dental pieces, tongue, and mucosal surfaces 5. Injection of 10 mL of 0.12% chlorhexidine into oral cavity 6. Aspiration of excess solution after 30 s 7. Brushing tooth by tooth on anterior and posterior surfaces and along the gumline with an electric toothbrush 8. Tongue brushing Procedure completed three times daily by nurses *Standard oral care*: 1. Head of bed elevated at 30° 2. Aspiration of oropharyngeal secretions 3. Adjustment of endotracheal cuff pressure 4. Gauze containing 20 mL of 0.12% chlorhexidine applied to all dental pieces, tongue, and mucosal surfaces 5. Injection of 10 mL of 0.12% chlorhexidine into oral cavity 6. Aspiration of excess solution after 30 s Procedure completed three times daily by nurses	Well described and all equal	The presence of new or progressive pulmonary opacities on CXR together with purulent respiratory secretions plus fever > 38°C or WBC > 10,000 cells/mL.Microbiological confirmation was defined by the presence of at least one potentially pathogenic organism in respiratory samples according to predefined thresholds (protected specimen brush yielding > 10^3 CFU/mL or tracheal aspirates yielding 10^5 CFU/mL)	VAP Days of mechanical ventilation-Hospital/ICU length of stay Ventilator-free days Antibiotic-free days ICU mortality Adverse events
Munro ($n = 547$)	Adult mechanically ventilated patients in medical, surgical or neurosurgical ICU. Mean age: 48 yrs; mean APACHE III: 73.1.	*Intervention 1: Toothbrushing* 1. Each tooth in each quadrant brushed for five strokes on the lingual, buccal, and biting surfaces with a soft pediatric toothbrush and toothpaste 2. Palate and tongue brushed 3. Each quadrant rinsed with 2.5 mL mouthwash using a transfer pipette 4. Excess saliva removed by suction 5. Moisturizing gel applied to all surfaces of the oral cavity and lips using a green toothette swab Procedure completed three times a day by nurses *Intervention 2: Chlorhexidine* 1. 5 mL of 0.12% solution of chlorhexidine gluconate by green toothettel swab to coat each tooth, the tongue, and the palateProcedure completed twice daily by nurses *Intervention 3: Toothbrushing and Chlorhexidine* As above Control (usual care): Not described	Not described	CPIS comprises 6 domains (temperature, WBC, tracheal secretions, oxygenation, CXR, and tracheal cultures); score > 6 was diagnosis of VAP	VAP at days 1 through 7

In this table, we present the trial characteristics.

CXR = chest radiograph; APACHE = Acute Physiology and Chronic Health Evaluation; WBC = white blood cell; CPIS= clinical pulmonary infection score; VAP = ventilator-associated pneumonia; CFU = colony-forming units; CDC = Centers for Disease Control and Prevention.

TABLE 2. Risk of Bias

Trial (Year)	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel
Lorente (2012)	Low risk of bias	Low risk of bias	High risk of bias
	Computer-generated random numbers sequences	Computer-generated random number table	Nurses aware of assignment
Prendergast (2012)	Low risk of bias	Low risk of bias	Unclear risk of bias
	Computer-generated random number sequences	Computer-generated random number sequences	No description, but likely unblinded
Biosca (2011)	High risk of bias	High risk of bias	Unclear risk of bias
	Sealed envelopes	Sealed envelopes	No description
Yao (2011)	Low risk of bias	Low risk of bias	Low risk of bias
	Computer-generated random number sequences	Computer-generated random number sequences	
Pobo (2009)	Low risk of bias	Unclear risk of bias	High risk of bias
	Computer-generated random number sequences	Sealed envelopes	Nurses aware of assignment
Munro (2009)	Low risk of bias	Low risk of bias	High risk of bias No blinding technique that was described

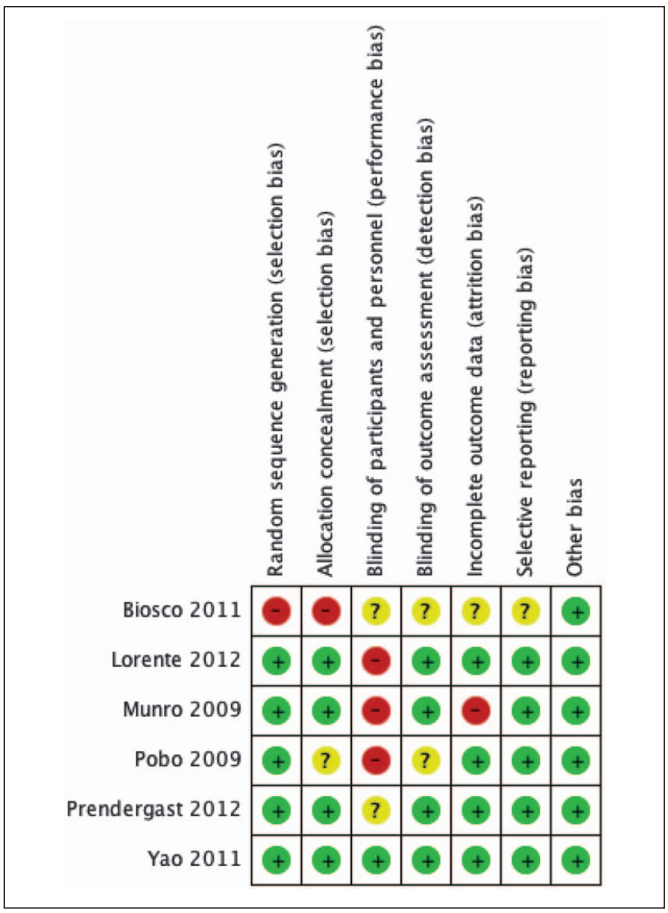

Figure 2. Summary of risk of bias.

DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimators (44).

Statistical heterogeneity was assessed by the I^2 statistic. Substantial heterogeneity was predefined as an $I^2 > 50\%$. All analyses were conducted in RevMan 5.1. We considered $p < 0.05$ to be statistically significant.

Subgroup Analyses

One subgroup analysis was planned a priori examining the difference between trials that used chlorhexidine as a part of oral care vs. trials that did not. We hypothesized that if toothbrushing were effective at VAP prevention, its effect may be attenuated when coadministered with chlorhexidine.

Sensitivity Analyses

We conducted two sensitivity analyses. The first was planned a priori, excluding trials at high risk of bias. We hypothesized that higher quality trials may demonstrate more modest treatment effects than trials of lower quality. The second sensitivity analysis was post hoc, excluding factorial design trials. We hypothesized that parallel group trials would show a greater treatment effect than trials including factorial designs.

RESULTS

Trial Identification

Our systematic search yielded 186 citations. One report was translated from Spanish to English to evaluate eligibility (37). Of 14 potentially eligible studies, we excluded one

Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias	Overall Risk of Bias
Low risk of bias	Low risk of bias	Low risk of bias (Identifier NCT01477099)	Low risk of bias	High
Low risk of bias Outcome assessors were blinded	Low risk of bias	Low risk of bias (Identifier NCT 00518752)	Low risk of bias	Unclear
Unclear risk of bias No description	Unclear risk of bias	Unclear risk of bias	Low risk of bias	High
Low risk of bias	Low risk of bias	Low risk of bias (Identifier NCT00604916)	Low risk of bias	Low
Unclear risk of bias Physicians and investigators were blinded	Low risk of bias	Low risk of bias (Identifier NCT00842478)	Low risk of bias	High
Low risk of bias Outcome assessors and adjudicators were blinded	High risk of bias (22% of data incomplete on VAP at day 3)	Low risk of bias (Identifier NCT00234598)	Low risk of bias	High

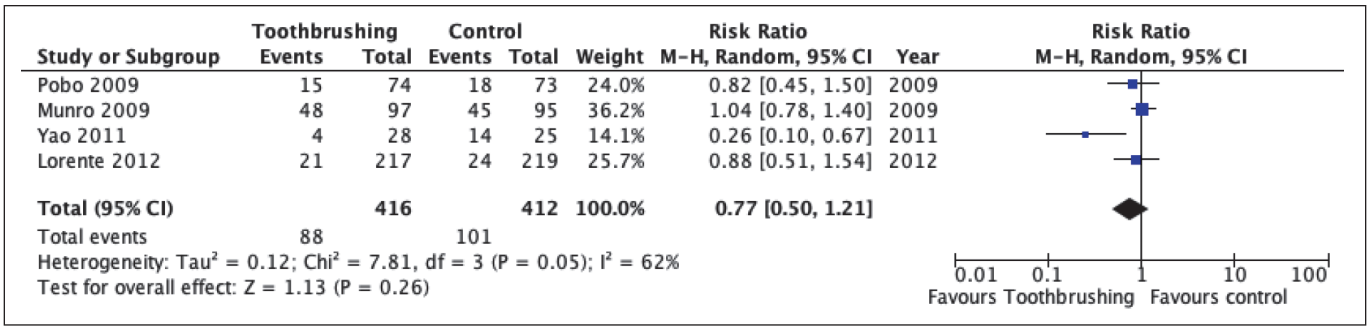

Figure 3. Outcome: ventilator-associated pneumonia. CI = confidence interval; M-H = Mantel-Haenszel.

study of toothbrushing which did not randomize patients (45); two studies that started as randomized trials but which became observationalstudies following low enrolment (46) or apparently large treatment effect (47), neither of which reported numerators or denominators; two trials that reported dental plaque but not VAP and that focused on the outcome of intracranial pressure (48, 49); and three trials using toothbrushing as part of a standard oral care protocol in both groups testing chlorhexidine vs. control (50, 51) or chlorhexidine vs. bicarbonate vs. control (52). Agreement on trial selection was 100%.

Figure 1 reflects the flow of articles. We identified six randomized trials for inclusion in this systematic review (37–41, 53). Of these, five compared toothbrushing with usual oral care for intubated patients (37–41); a sixth compared an electric toothbrush to a manual toothbrush (53).

Trial Characteristics

In **Table 1**, we describe characteristics of the six trials that enrolled medical (37, 39–41), surgical (37, 39–41), neurosurgical(38, 39, 53), and trauma (37, 39, 41) patients. Only one was multicentered (40). The definition of VAP varied. One trial was not explicit (e.g., VAP was identified "according to clinical, medical and microbiological criteria") and reported cases of VAP per 1,000 ventilator days, precluding pooling with the other trials (37). We were unable to obtain further information from authors.

Risk of Bias

In **Table 2**, we report the Cochrane risk of bias tool, whereby trials were judged to be at high, unclear, or low risk of bias. The overall risk of bias was low in one trial (38), unclear in one trial (53), and high in four trials (37, 39–41), shown in **Figure 2**.

TABLE 3. Summary of Findings

Toothbrushing for Prevention of Ventilator-Associated Pneumonia Patient or Population: Mechanically Ventilated Patients at Risk of Pneumonia Setting: ICU Intervention: Toothbrushing						
	Illustrative Comparative Risks[a] (95% Confidence Interval)					
	Assumed Risk	Corresponding Risk				
Outcomes	Control	Tooth Brushing	Relative Effect (95% Confidence Interval)	No. of Participants (Studies)	Quality of the Evidence (Grade)	Comments
Ventilator-associated pneumonia Clinical and microbiological measures	Study population 245 per 1000	189 per 1000 (123–297)	Risk ratio 0.77 (0.50 to 1.21)	828 (four studies)	⊕⊖⊖⊖ Very low[b,c,d]	
	Moderate 50 per 1000	38 per 1000 (25–61)				
	High 100 per 1000	77 per 1000 (50–121)				

GRADE Working Group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: very uncertain about the estimate.

[a]The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval [CI]) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Three trials were at high risk of bias, mainly due to lack of, or inappropriate, blinding.

[c]Heterogeneity was high $I^2 = 62\%$.

[d]95% CI (0.50–1.21), imprecision demonstrated with a wide CI that ranged between a relative risk reduction of 50% and a relative risk increase of 21% in ventilator-associated pneumonia.

Ventilator-Associated Pneumonia

Patients who developed VAP were reported in four trials enrolling 828 patients that compared toothbrushing with no toothbrushing (38–41). Pooling these results, there was a trend toward lower VAP rates (RR, 0.77; 95% CI, 0.50–1.21; $p = 0.26$; substantial heterogeneity $I^2 = 62\%$; **Fig. 3**). There was also a trend toward lower VAP rates in the trial not included in the main meta-analysis because dichotomous outcomes were not reported (20.68 vs. 25.89 cases per 1,000 ventilator days, $p = 0.53$) in one trial comparing toothbrushing vs. no toothbrushing (37).

In the trial comparing electric toothbrushing to manual toothbrushing, VAP rates were eight of 20 (40.0%) vs. ten of 24 (42.0%), respectively, with no difference in VAP (RR, 0.96; 95% CI, 0.47–1.96; $p = 0.91$) (53).

Mortality

In the only trial reporting ICU mortality (41), among 436 patients, toothbrushing did not significantly influence ICU mortality (toothbrushing 62 of 217 [28.6%] vs. control 69 of 219 [31.5%]; RR, 0.91; 95% CI, 0.68–1.21; $p = 0.50$). In the trial that reported hospital mortality (147 patients) (39), toothbrushing did not significantly reduce hospital mortality (toothbrushing 16 of 74 [21.6%], control 23 of 73 [31.5%]; RR, 0.69; 95% CI, 0.40–1.19; $p = 0.18$).

ICU Length of Stay

When the data from the two trials reporting ICU length of stay (38, 41) were aggregated, toothbrushing had no effect on ICU length of stay (mean difference, −0.98 days; 95% CI, −3.30 to 1.33, $p = 0.40$; no heterogeneity $I^2 = 0\%$).

Subgroup Analyses

As hypothesized, the subgroup analysis showed that in one trial (38), which did not use chlorhexidine as a part of oral care, as hypothesized, VAP was significantly lower (RR, 0.26; 95% CI, 0.10–0.67; $p = 0.006$), whereas trials (39, 41) using chlorhexidine in both groups did not show a significant impact on VAP (RR, 0.85; 95% CI, 0.57–1.29; $p = 0.45$; interaction p value = 0.02).

Sensitivity Analyses

The first sensitivity analysis excluded trials at high or unclear risk of bias. Only one trial was at low risk of bias (38); contrary to our hypothesis, results suggested that the use of toothbrushing is associated with significant reduction in VAP (RR, 0.26; 95% CI, 0.10–0.67; $p = 0.006$).

The second sensitivity analysis excluding factorial designs (40) assuming an interaction between chlorhexidine and toothbrushing showed, as hypothesized, a trend toward lower rates of VAP (relative risk, 0.64; 95% CI, 0.34–1.20; $p = 0.16$; low heterogeneity $I^2 = 16\%$).

DISCUSSION

In this systematic review, we found that toothbrushing was associated with a trend toward lower VAP rates; however, in the single trial at low risk of bias, the VAP reduction was significant (38). The trial comparing electric and manual toothbrushing did not suggest a significant difference with respect to VAP (53). Toothbrushing had no significant effect on ICU length of stay, or ICU or hospital mortality, although most trials did not report these outcomes.

There are limitations to the data included in this review (**Table 3**). Although we incorporated all randomized trials relevant to our objective, due to the small number of included trials, we could not use funnel plot symmetry to assess for publication bias (54). The VAP definitions were variable, and one trial did not clearly define VAP (37). Inferences about the effect on VAP are limited by statistical heterogeneity when four trials are pooled, reflected in an I^2 of 62%. In the trial with low risk of bias, VAP was significantly reduced, but inferences are limited due to low event rates and a small sample size (38). This trial was the only trial that did not incorporate chlorhexidine as part of oral care. It is possible that use of chlorhexidine in all the other trials diminished the clinical effect of toothbrushing, as supported by the significant subgroup difference between trials that used chlorhexidine vs. the trial that did not, which partly explains the heterogeneity of the overall pooled findings.

Strengths of this systematic review include the comprehensive search strategy using seven databases, explicit inclusion and exclusion criteria, and the Cochrane risk of bias assessment for each outcome and overall for each trial (42). We followed the PRISMA guidelines for reporting systematic reviews (55). Trial selection, quality assessment, data abstraction, and data analysis were conducted in duplicate. We used the conservative random effects model to pool results across trials.

Low-grade recommendations suggesting toothbrushing for intubated adults exist in the nursing literature (15, 56–58). Toothbrushing is not mentioned in existing VAP prevention guidelines (59–62). Nonetheless, surveys suggest that toothbrushing is time-consuming and that nurses want more specific training, in that it is not as straightforward as it looks (16–18, 20, 22, 23, 63). Indeed, current approaches vary, partly related to no clearly superior frequency or technique in this population, which merit further investigation. Whether there are adverse effects in certain populations is unclear (e.g., bacteremia induced in immunocompromised patients with gingivitis [64, 65]). Nevertheless, we believe that a conceptual shift is worth considering—away from considering toothbrushing as only an approach to comfort and hygiene—toward a potentially important nosocomial infection prevention strategy.

Although the effect of toothbrushing on dental plaque in various settings has been demonstrated, more robust evidence would be welcome regarding the outcome of VAP. According to clinicaltrials.gov, there are two additional trials in the prepublication phase. The first (NCT00521677) compares oral care with and without toothbrushing in Israel (now completed). The second (NCT01446874) compares toothbrushing and a polyurethane endotracheal tube with subglottic secretion vs. standard care in thoracic surgery patients in the United States (currently recruiting). According to controlled-trials.com, a third trial (ISRCTN89147541) comparing twice vs. four times daily toothbrushing on bacterial colonization in the upper respiratory tract is ongoing in the United Kingdom (registered in 2006). Further research on this aspect of oral care is needed, particularly in the presence and absence of other effective VAP prevention strategies, in the context of oropharnygeal vs. nasal feeding tubes and gastric vs. small bowel feeding. In edentulous patients, the role of brushing other oral surfaces with antiseptic agents is worth further investigation. We look forward to future multicenter trials to maximize the precision and generalizability of the findings.

In summary, randomized trials to date show that toothbrushing is associated with a trend toward lower rates of VAP in intubated, mechanically ventilated critically ill patients. There is no clear difference between electric and manual toothbrushing. Toothbrushing has no effect on ICU mortality, hospital mortality, or ICU length of stay.

ACKNOWLEDGMENTS

We appreciate the help of Drs. Prendergast and Scannapieco who kindly provided additional study information. We also acknowledge Dr. Amiram Lev who responded to our request for a trial update. We thank David Lightfoot for his help searching the literature. We are grateful to Elaine Stockler-Leite and Dr. Claudia dos Santos for their translation assistance.

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