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Association Between Daily Toothbrushing and Hospital-Acquired Pneumonia
A Systematic Review and Meta-Analysis

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IMPORTANCE Hospital-acquired pneumonia (HAP) is the most common and morbid health care–associated infection, but limited data on effective prevention strategies are available.

OBJECTIVE To determine whether daily toothbrushing is associated with lower rates of HAP and other patient-relevant outcomes.

DATA SOURCES A search of PubMed, Embase, Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials, Web of Science, Scopus, and 3 trial registries was performed from inception through March 9, 2023.

STUDY SELECTION Randomized clinical trials of hospitalized adults comparing daily oral care with toothbrushing vs regimens without toothbrushing.

DATA EXTRACTION AND SYNTHESIS Data extraction and risk of bias assessments were performed in duplicate. Meta-analysis was performed using random-effects models.

MAIN OUTCOMES AND MEASURES The primary outcome of this systematic review and meta-analysis was HAP. Secondary outcomes included hospital and intensive care unit (ICU) mortality, duration of mechanical ventilation, ICU and hospital lengths of stay, and use of antibiotics. Subgroups included patients who received invasive mechanical ventilation vs those who did not, toothbrushing twice daily vs more frequently, toothbrushing provided by dental professionals vs general nursing staff, electric vs manual toothbrushing, and studies at low vs high risk of bias.

RESULTS A total of 15 trials met inclusion criteria, including 10 742 patients (2033 in the ICU and 8709 in non-ICU departments; effective population size was 2786 after shrinking the population to account for 1 cluster randomized trial in non-ICU patients). Toothbrushing was associated with significantly lower risk for HAP (risk ratio [RR], 0.67 [95% CI, 0.56-0.81]) and ICU mortality (RR, 0.81 [95% CI, 0.69-0.95]). Reduction in pneumonia incidence was significant for patients receiving invasive mechanical ventilation (RR, 0.68 [95% CI, 0.57-0.82) but not for patients who were not receiving invasive mechanical ventilation (RR, 0.32 [95% CI, 0.05-2.02]). Toothbrushing for patients in the ICU was associated with fewer days of mechanical ventilation (mean difference, −1.24 [95% CI, −2.42 to −0.06] days) and a shorter ICU length of stay (mean difference, −1.78 [95% CI, −2.85 to −0.70] days). Brushing twice a day vs more frequent intervals was associated with similar effect estimates. Results were consistent in a sensitivity analysis restricted to 7 studies at low risk of bias (1367 patients). Non-ICU hospital length of stay and use of antibiotics were not associated with toothbrushing.

CONCLUSIONS The findings of this systematic review and meta-analysis suggest that daily toothbrushing may be associated with significantly lower rates of HAP, particularly in patients receiving mechanical ventilation, lower rates of ICU mortality, shorter duration of mechanical ventilation, and shorter ICU length of stay. Policies and programs encouraging more widespread and consistent toothbrushing are warranted.

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Invited Commentary
Multimedia
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Hospital-acquired pneumonia (HAP) is the most common and morbid nosocomial infection. It affects approximately 1% of hospitalized patients and is associated with increased mortality, longer length of stay, and higher costs.[1-4] While the risk per patient is higher for intubated patients receiving mechanical ventilation, most cases of nosocomial pneumonia occur in nonintubated patients by virtue of their greater numbers in the hospital population. Crude and adjusted mortality rates associated with nonventilator HAP (NV-HAP) are similar to those of ventilator-associated pneumonia (VAP).[2-5]

Despite the frequency and morbidity of HAP, little consensus exists on how best to prevent it. Experts advocate rigorous oral care, as HAP is believed to be triggered by microaspiration or macroaspiration of oral flora, a hypothesis supported by studies documenting that microaspirations are common in hospitalized patients and sequencing studies documenting parity between organisms isolated from the mouth and lungs.[6-8] Many nursing bundles, particularly for patients receiving mechanical ventilation, include oral care with the antiseptic chlorhexidine to reduce microbial burden in the oral cavity. However, the use of chlorhexidine for oral care is controversial since some studies suggest a possible association with higher mortality rates.[9-12] Furthermore, it is not clear whether chlorhexidine prevents pneumonia: a meta-analysis of double-blinded randomized clinical trials[12] showed no association between oral care with chlorhexidine and lower VAP rates, and a cluster randomized trial investigating the discontinuation of chlorhexidine[13] found that comprehensive oral care without chlorhexidine was associated with similar rates of infection-related ventilator-associated complications compared with oral care with chlorhexidine.

Rigorous, regular toothbrushing is an alternative strategy to decrease microbial burden in the mouth without the potential risk associated with oral chlorhexidine. Indeed, toothbrushing may be more effective than antiseptics at reducing microbial burden, since mechanical scrubbing may better disrupt plaque and other biofilms compared with antiseptics.[14,15] Prevention guidelines, however, have traditionally not emphasized toothbrushing, and consequently, practices vary widely between hospitals.[16-18] The latest guidelines from the Society for Healthcare Epidemiology of America recommend "daily oral care with toothbrushing but without chlorhexidine"[19] based on 2 meta-analyses[20,21] that reported toothbrushing was associated with significantly lower VAP rates, shorter duration of mechanical ventilation, and shorter ICU stay. These meta-analyses were small, however, and did not include many recent and potentially pertinent studies. In addition, other meta-analyses[22-24] have reported no association between toothbrushing and pneumonia. Therefore, we conducted an updated meta-analysis of randomized clinical trials assessing the association of toothbrushing with HAP, mortality, length of stay, duration of mechanical ventilation, and use of antibiotics.

Key Points

Question Is daily toothbrushing among hospitalized patients associated with prevention of hospital-acquired pneumonia and improved objective outcomes?

Findings This systematic review and meta-analysis of 15 randomized clinical trials with an effective population size of 2786 patients found that hospital-acquired pneumonia rates were lower among patients randomized to daily toothbrushing, particularly among patients receiving invasive mechanical ventilation. Toothbrushing was also associated with shorter duration of mechanical ventilation, shorter intensive care unit (ICU) length of stay, and lower ICU mortality, whereas hospital length of stay and use of antibiotics showed no differences.

Meaning These findings suggest that daily toothbrushing may be associated with lower rates of pneumonia and ICU mortality, particularly among patients undergoing invasive mechanical ventilation; programs and policies to encourage daily toothbrushing are warranted.

Methods

Protocol and Registration

The protocol for this systematic review and meta-analysis was registered with PROSPERO (CRD42023392906). The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (eTable 1 in Supplement 1) and the Cochrane Handbook of Systematic Reviews of Interventions, version 6.3.[25]

Identification of Studies

We searched the PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, Scopus, and Cumulative Index to Nursing and Allied Health databases from inception through March 9, 2023. We also searched 3 trial registries: ClinicalTrials.gov, the International Standard Randomized Controlled Trial Number Registry, and the International Clinical Trials Registry Platform. We further searched the reference lists of articles that met inclusion criteria and recent review articles[20,21,24,26-29] and queried Google Scholar for similar articles for all included studies. No date or language restrictions were applied.

Search Strategy

The primary search strategy was developed for PubMed with the support of a medical information specialist. It included a combination of Medical Subject Heading terms and keywords related to toothbrushing and HAP and was adapted as needed for each database and registry (eMethods 1 in Supplement 1).

Eligibility Criteria

Studies meeting the following criteria were eligible: (1) randomized clinical trials; (2) adult participants 16 years or older in acute care hospitals; (3) investigation of the effects of toothbrushing vs no toothbrushing; and (4) inclusion of at least 1 of the following outcomes: HAP (VAP and/or NV-HAP), duration of mechanical ventilation, ICU length of stay, hospital length of stay, mortality, or use of antibiotics. An overview of excluded studies, including reasons for exclusions, is provided in eTable 2 in Supplement 1.

Study Selection and Data Extraction

Two reviewers (S.E. and M.K.) independently screened all titles and abstracts to assess eligibility. Full-text articles from potentially eligible studies were further reviewed for inclusion. Discrepancies between reviewers were resolved through discussion and consensus. Study selection and data extraction were performed using Covidence software and a standardized data extraction form.[30] Data were extracted by the 2 reviewers independently, and inconsistencies were resolved through consensus discussions. Extracted data included study characteristics, intervention and control group procedures, funding sources, HAP rates, mortality, hospital length of stay, ICU length of stay, duration of mechanical ventilation, and use of antibiotics (data collection form in eMethods 2 in Supplement 1). When primary outcome data were incomplete or inconsistently reported, authors were contacted for clarification. The study was excluded if no response was received within 4 weeks and clarification was necessary to determine study eligibility. If a study included multiple groups, only pertinent groups were extracted.[31,32]

Risk of Bias and Quality Assessment

Both reviewers (S.E. and M.K.) independently assessed risk of bias in all included studies using the Cochrane risk of bias template for randomized clinical trials.[33] Inconsistencies were resolved through consensus discussions. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used to evaluate certainty of evidence and strength of recommendations.[34]

Quantitative Data Analysis and Subgroup Analyses

Data were synthesized using inverse-variance random-effects models. Effect sizes were expressed as risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes with 95% CIs. We used RevMan Web to conduct the analyses.[35] Heterogeneity was assessed using the I^2 statistic and χ^2 test. A funnel plot was created and the Egger test was performed to quantify asymmetry using the metafor[36] package in RStudio, version 4.2.2.[37] Prespecified subgroup analyses included patients receiving invasive mechanical ventilation vs those who were not, toothbrushing 2 times vs 3 or more times daily, toothbrushing provided by a dental professional vs general nursing staff, electrical vs manual toothbrushing, and low vs high risk of bias studies. These steps were performed in accordance with the Cochrane Handbook.[25]

Results

Description of Included Studies

A PRISMA flowchart depicting the study selection process is shown in **Figure 1**.[38] The search strategy identified 825 studies after removing duplicates; 101 were selected for full-text review based on title and abstract. Of these, 15 studies met inclusion criteria (11 were derived from databases,[31,39-48] 1 from a registry,[32] and 3 through manual review of references or Google Scholar[49-51]). The **Table** summarizes included studies. Three studies were conducted in Iran,[32,39,40] 3 in Brazil,[41,42,51] 2 in India,[43,44] 2 in Spain,[45,46] 2 in China,[31,50] and 1 each in the US,[47] Malaysia,[49] and Taiwan.[48] Most studies were in English,[40-49] 1 was translated from Portuguese,[51] 2 from Chinese,[31,50] and 2 from Persian.[32,39] Study publication dates spanned 2009 to 2022. One study was a doctoral dissertation.[51] One study was a cluster trial that randomized hospital wards rather than patients to intervention vs control groups.[47] We calculated effective sample sizes for this study using the intracluster correlation coefficient per the Cochrane Handbook (eMethods 3 in Supplement 1). Follow-up among all studies varied from 5 to 28 days or until pneumonia diagnosis, extubation, or discharge. Three studies only followed up patients for pneumonia for 5 days.[31,32,39] In most studies, teeth were brushed 2 times[39-41,43,48] or 3 times[32,44-46,49-51] daily, ranging from 4 to 5 times a week[42] to 4 times daily.[31,47]

Quality Assessment

Study quality assessments are summarized in **Figure 2**. Eight of the 15 included studies[31,32,39,43,45,47,49,50] were deemed at high or unclear risk of bias. None of the studies was truly double blinded, given the difficulty concealing toothbrushing from the practitioners performing toothbrushing or patients. However, we identified 10 studies[32,39-42,44-46,48,51] where the investigators assessing outcomes were blinded to patients' group assignments. Taking into account bias in all domains, 7 studies[41,42,44-46,48,51] were deemed at low risk of bias.

Publication bias was assessed among studies reporting on HAP. We did not assess for publication bias using other outcomes because the Cochrane Handbook does not recommend asymmetry assessment with less than 10 studies. A funnel plot using HAP as the outcome (eFigure 1 in Supplement 1) visually suggested asymmetry, indicating possible small study effect or publication bias, but regression test results for funnel plot asymmetry were not significant ($z = -0.75$; $P = .45$), suggesting no evidence of small study effects or publication bias.[60]

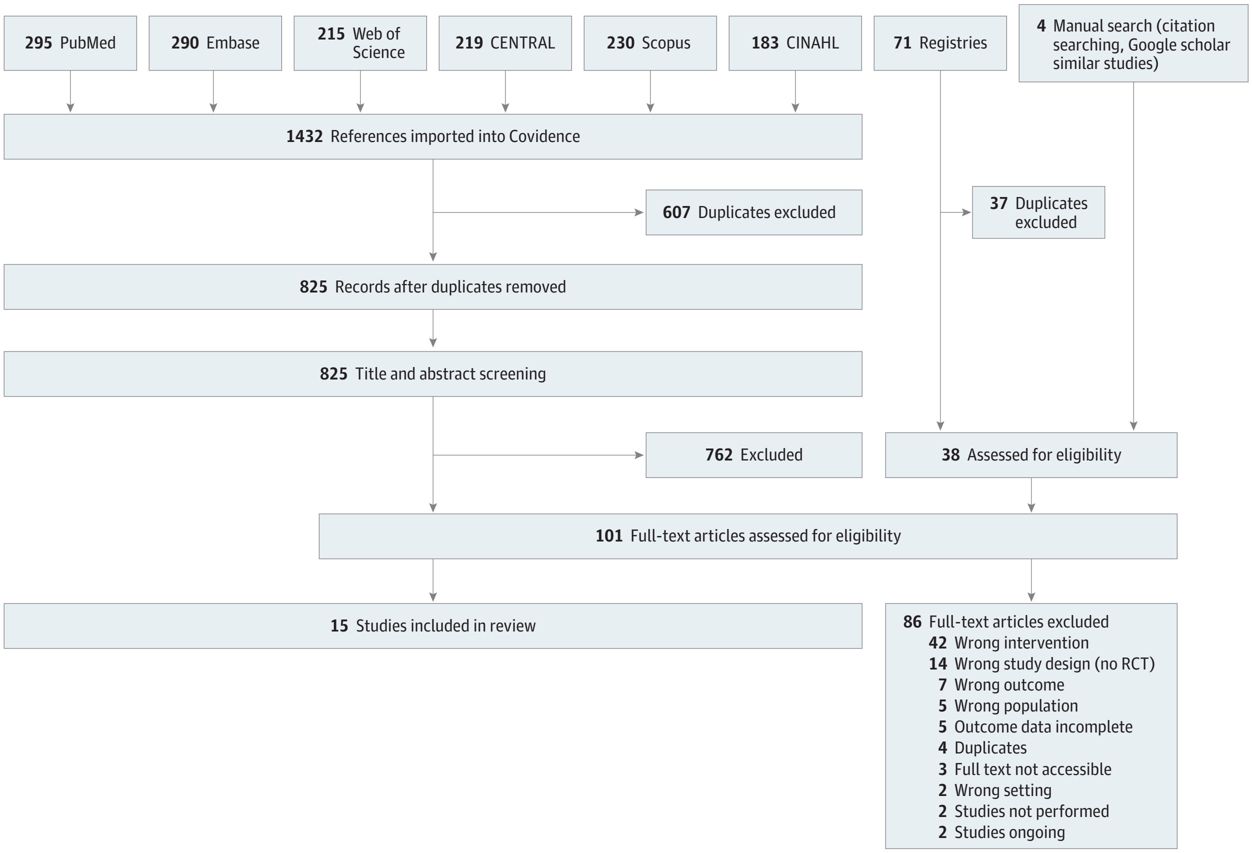
Participants

Among the 15 studies that met inclusion criteria, including 10 742 patients, 13 studies[31-41,43-46,48-51] included patients receiving mechanical ventilation in the ICU, 1 included hospitalized patients who were not receiving invasive mechanical ventilation,[47] and 1 included patients in the ICU receiving and not receiving mechanical ventilation.[42] In total, there were 2033 ICU patients and 8097 non-ICU patients. After reducing the cluster randomized trial[47] from 8709 patients to an effective sample size of 753, the total number of patients included in the meta-analysis was 2786. Most studies included only patients with oral or nasal intubation; in 1 study,[45] 19% of patients had tracheotomies.

Adjunctive Interventions

Chlorhexidine gluconate was used in both the toothbrushing and the control groups in 11 studies.[32,39-46,49,51] The remaining studies used plaque-removing toothpaste,[47] saline,[31] povidone-iodine,[50] or purified water[48] in both study groups.

Figure 1. Study Flowchart



CENTRAL indicates Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health, RCT, randomized clinical trial.

Adverse Events

Four studies[42,44,46,49] reported on adverse events. One study[42] reported that patients randomized to toothbrushing had more mucosal irritation and minor intraoral bleeding compared with patients in the control group but there were no major adverse events leading to exclusion. The other 3 studies reported no adverse events.[44,46,49]

Incidence of HAP (VAP and NV-HAP)

Thirteen studies (2557 patients)[31,32,39,41-49,51] included data on HAP (including both VAP and NV-HAP). Patients randomized to toothbrushing had significantly lower HAP rates (RR, 0.67 [95% CI, 0.56-0.81]; I^2 = 0%) (**Figure 3**). Twelve studies reported on VAP (1744 patients).[31,32,39,41-46,48,49,51] Toothbrushing was associated with significantly lower VAP rates (RR, 0.68 [95% CI 0.57-0.82]; I^2 = 0%), corresponding to a number needed to treat of 12 to prevent 1 VAP case. Two studies reported on NV-HAP (n = 813).[42,47] One of these studies included patients in the ICU who did not receive invasive mechanical ventilation (n = 60).[42] The other was a non-ICU cluster randomized trial (effective sample size, 753 patients) (eMethods 3 in Supplement 1).[47] The cluster randomized trial reported a significant reduction in NV-HAP in medical units (85% risk reduction [P = .002]) but not in surgical units (56% risk reduction [P = .29]). On meta-analysis of the 2 studies with NV-HAP data, RR was 0.32 (95% CI, 0.05-2.02; I^2 = 0%).

Findings were similar on sensitivity analysis limited to the 7 studies with low risk of bias (1367 patients),[41,42,44-46,48,51] all of which focused on patients in the ICU (RR, 0.64 [95% CI, 0.48-0.85]; I^2 = 8%). Findings were also similar in 5 studies at low risk of bias[41,42,44,46,51] that followed up patients through extubation or 28 days (RR, 0.64 [95% CI, 0.46-0.90]) and in a sensitivity analysis using a fixed-effects model to avoid overweighting small studies.

Results were similar with 2 times daily toothbrushing (RR, 0.63 [95% CI, 0.44-0.91]), 3 times daily toothbrushing (RR, 0.77 [95% CI, 0.53-1.11]), and 4 times daily toothbrushing (RR, 0.69 [95% CI, 0.33-1.43]) (eFigure 2 in Supplement 1). This finding was consistent among 6 studies at low risk of bias[41,44-46,48,51] (RR for 2 times daily toothbrushing, 0.44 [95% CI, 0.19-1.03]; RR for 3 times daily toothbrushing, 0.81 [95% CI, 0.56-1.18]).

Mortality

None of the studies reported on hospital mortality, but 6 studies reported on ICU mortality (n = 1331 patients).[41-43,45,46,50] Toothbrushing was associated with significantly lower ICU mortality (RR, 0.81 [95% CI, 0.69-0.95]; I^2 = 0%) (**Figure 4**).

Table. Characteristics of Included Studies

Source	Country	No. of patients	Setting	Procedure: Intervention	Procedure: Control	Pneumonia definition	End of follow-up	Blinded outcome assessors
Bellissimo-Rodrigues et al,[42] 2014	Brazil	254	ICU	Thrice-daily routine care and toothbrushing 4-5 times/wk performed by a dental surgeon with soft child toothbrush, tongue scraping, calculus removal, atraumatic restorative treatment of caries, teeth extraction, and oral application of chlorhexidine	Thrice-daily oral care by oral cavity cleaning with spatula wrapped in gauze, followed by topical application chlorhexidine, 0.12% or 0.2% (depending on consciousness)	VAP and NV-HAP defined by CDC's NHSN surveillance definition of health care-associated infection (according to CDC)[52]	48 h After ICU discharge	Yes
Chacko et al,[44] 2017	India	206	ICU	Thrice-daily toothbrushing and tongue brushing with chlorhexidine, 0.2%, in the oral cavity	Thrice-daily oral care by swabbing with sponges soaked in chlorhexidine, 0.2%	VAP defined as patient receiving ventilation; abnormal chest radiographic finding suggestive of pneumonia; fever or hypothermia; leukopenia or leukocytosis; purulent endotracheal aspirate or increased respiratory secretions or suction; worsening gas exchange or increasing oxygen demand (if only the last 2 are present, then positive culture yield needed according to CDC guidelines valid in 2014)	ICU discharge	Yes
de Lacerda Vidal et al,[41] 2017	Brazil	213	ICU	Twice-daily toothbrushing and brushing of all surfaces, tongue, and mucosal surface of the mouth with a toothbrush with small and soft bristles, and dental gel based on chlorhexidine, 0.12%	Twice-daily oral care by swabbing all tooth surfaces, tongue, and mucosal surfaces of the mouth and applying chlorhexidine, 0.12%, oral solution	Suspected VAP defined as new or progressive pulmonary infiltrate on chest radiographic finding and ≥2 of 3 clinical criteria (fever, leukocytosis or leukopenia, purulent respiratory secretions). Confirmed VAP defined as bacterial growth of endotracheal aspirates and bronchoalveolar lavage with values $\geq 10^6$ CFU/mL and $\geq 10^4$ CFU/mL (according to the American Thoracic Society)[53]	Day 28, death, extubation, or ICU discharge	Yes
Falahinia et al,[39] 2016	Iran	68	ICU	Twice-daily toothbrushing with soft child toothbrush and chlorhexidine, 0.2%, for 3 min	Twice-daily oral care with gauze swab soaked in chlorhexidine, 0.2%	VAP defined as CPIS ≥6, including the parameters temperature, leukocytes, tracheal secretions, blood oxygenation, chest radiographic results, and tracheal aspirate culture (according to Pugin et al)[54]	5 d (Duration of intervention)	Yes
Félix,[51] 2016	Brazil	58	ICU	Twice-daily toothbrushing with toothbrush soft bristles soaked in chlorhexidine, 0.12%	Twice-daily oral care with gauze soaked in chlorhexidine, 0.12%	VAP defined by Diagnostic Criteria for Healthcare-Related Infections (according to National Brazil Guidelines)[55]	Extubation, VAP diagnosis	Yes
Giuliano et al[47] 2021	US	8709 (Effective sample size, 753)	2 Medical and 2 surgical wards (Cluster RCT)	Toothbrushing 4 times/d with soft toothbrushes with plaque-removing toothpaste as provided to patients (target frequency[a])	Patients were not reminded to brush their teeth, no oral care supplies were provided	NV-HAP defined by radiological diagnosis, cultures when available, and symptom assessment (according to CDC)[56]	Hospital discharge	No
Gong et al,[31] 2018	China	80[b]	ICU	Toothbrushing 4 times/d with soft toothbrush dipped in saline, brushing of tongue, each tooth, and interdental space with gentle movement	Oral care 4 times/d by using saline on teeth, tongue, throat, cheeks, and jaw	VAP defined by Intensive Care Branch of Chinese Medical Association[57]	5 d (Duration of intervention)	Unclear
Khan et al,[49] 2017	Malaysia	9	ICU	Thrice-daily toothbrushing with chlorhexidine, 0.2%	Thrice-daily oral care with chlorhexidine, 0.2%, foam swab	VAP defined by physician and ICU nursing staff	11 d (Duration of intervention)	Unclear
Long et al[50] 2012	China	61	ICU	Thrice-daily toothbrushing with a soft child toothbrush, preceded by povidone, 0.1%-iodine gauze scrubbing before intubation	Thrice-daily oral care by scrubbing teeth and buccal area with povidone, 0.1%-iodine swab	VAP defined by positive culture of secretions of lower respiratory tract[c]	Extubation	Unclear

(continued)

Table. Characteristics of Included Studies (continued)

Source	Country	No. of patients	Setting	Procedure: Intervention	Procedure: Control	Pneumonia definition	End of follow-up	Blinded outcome assessors
Lorente et al,[45] 2012	Spain	436	ICU	Thrice-daily toothbrushing (tooth by tooth on anterior and posterior surfaces, gumline, and tongue for 90 s) with a brush soaked in chlorhexidine, 0.12%, preceded by oral care with gauze soaked in chlorhexidine, 0.12%	Thrice-daily oral care with gauze soaked in chlorhexidine, 0.12%	VAP defined by all fulfilled: new onset of bronchial purulent sputum, temperature >38 °C or <35.5 °C, leukocytosis and/or leukopenia, chest radiograph with new or progressive infiltrates, significant quantitative culture of respiratory secretions by tracheal aspirate	7 d for VAP outcome	Yes
Nasiriani et al,[40] 2016	Iran	168	ICU	Twice-daily toothbrushing and tongue brushing with soft child toothbrush and distilled water; a swab with chlorhexidine was then rubbed on the tongue, followed by normal saline	Thrice-daily oral care by mouth rinsing with normal saline and rubbing a swab with chlorhexidine on the tongue	VAP defined as CPIS ≥6[d] including the parameters temperature, leukocytes, tracheal secretions, blood oxygenation, chest radiographic results, and tracheal aspirate culture (according to Pugin et al)[54]	5 d (Duration of intervention)	Yes
Pobo et al,[46] 2009	Spain	147	ICU	Thrice-daily toothbrushing tooth by tooth on anterior and posterior surfaces, along the gumline and the tongue with electric toothbrush, followed by oral care with chlorhexidine, 0.12%, same as the control group	Thrice-daily oral care with chlorhexidine, 0.12%-soaked gauze to all teeth, tongue, and mucosal surface and injection of chlorhexidine, 0.12%, into the oral cavity which is aspirated after 30 s	Suspected VAP defined by new or progressive pulmonary opacities, purulent respiratory secretions, and fever or leukocytosis; confirmed VAP defined by presence of ≥1 potentially pathogenic organism in respiratory samples according to predefined thresholds	28 d	Yes
Salarzehi et al,[32] 2021	Iran	60[e]	ICU	Thrice-daily toothbrushing for 5 min all the outer and inner surfaces of the teeth and gums and then the tongue and palate surfaces with an infant toothbrush and antimicrobial toothpaste containing fluoride by making rotating movements or moving from the back to the front of the mouth; each part of the mouth was then cleaned with sterile distilled water; mouth, tongue, and teeth were then rinsed with a chlorhexidine, 0.2%-soaked swab	Oral care with chlorhexidine, 0.2%, mouthwash (no frequency reported for control group)	VAP defined as modified CPIS ≥5, including the parameters temperature, leukocytes, tracheal secretions, blood oxygenation, and chest radiographic results (according to Lauzier et al)[58]	5 d (Duration of intervention)	Yes
Singh et al,[43] 2022	India	220	ICU	Twice-daily toothbrushing with ultrasoft toothbrush (gauze wrapped around fingers if brushing was not possible), lubrication of oral mucosa, and chlorhexidine, 0.2%, mouthwash	Oral care with chlorhexidine, 0.2%, mouthwash; frequency according to BOAS score	Suspected VAP defined by fever, positive ETT cultures, chest auscultation, increased ventilator demand, or new abnormal chest radiographic findings	VAP, death, or discharge	Unclear
Yao et al,[48] 2011	Taiwan	53	ICU	Twice-daily toothbrushing the teeth's facial sides with an electric toothbrush, moisturizing the oral cavity with purified water, cleansing lingual sides and massaging tongue, gums, and mucosa with a soft child toothbrush; cleaning oral cavity with oral swab connected to the suction tube and rinsing with purified water (duration 15-20 min) and daily usual oral care	Once-daily usual oral care with oral swabs or cotton swabs and twice daily mock care for 10-15 min; lips were moisturized using an oral swab with purified water	VAP defined as modified CPIS >6, including the parameters temperature, leukocytes, tracheal secretions, blood oxygenation, chest radiographic results, progression of pulmonary infiltrate, and tracheal aspirate culture (according to Singh et al)[59]	9 d (7 d Intervention)	Yes

Abbreviations: BOAS, Beck Oral Assessment Scale; CDC, Centers for Disease Control and Prevention; CFU, colony-forming unit; CPIS, Clinical Pulmonary Infection Score; ETT, endotracheal tube; ICU, intensive care unit; NHSN, National Healthcare Safety Network; NV-HAP, nonventilator hospital-associated pneumonia; RCT, randomized clinical trial; VAP, ventilator-associated pneumonia.

[a] The target frequency of toothbrushing 4 times/d was not met in any of the intervention units but was significantly higher than on any of the control units.

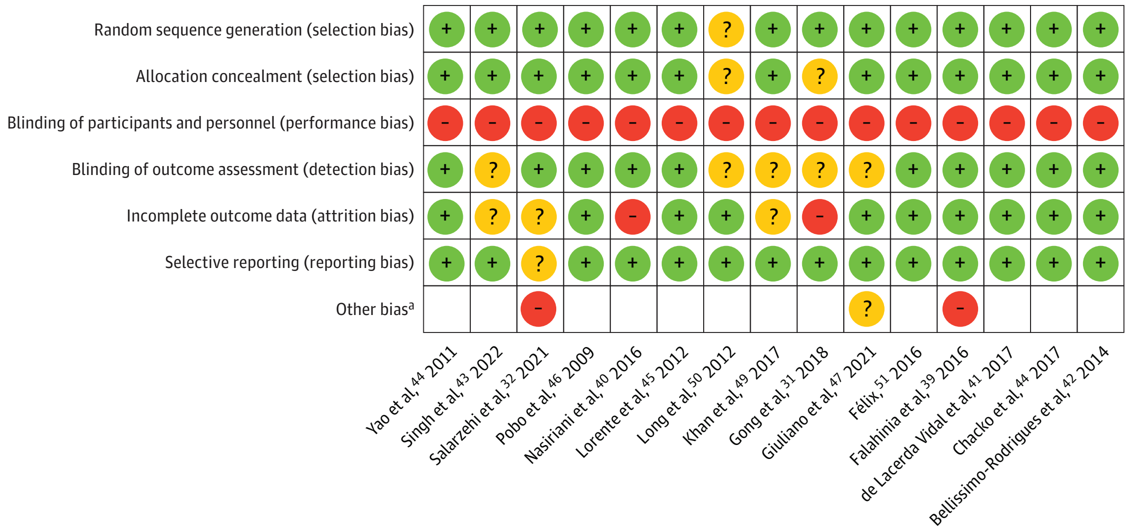
[b] The study was conducted with 3 groups (n = 120). The third group (n = 40) was excluded as it contained a traditional Chinese medicine intervention and was not relevant to our study question.

[c] Because pneumonia was defined only by positive culture yield, this study was excluded from the pneumonia meta-analysis and analyzed only for the outcomes of duration of ventilation and mortality.

[d] Because pneumonia was assessed and reported on multiple days defined by a CPIS value of 6 or more, a cumulative total number of pneumonia cases could not be extracted. Therefore, this study was excluded from the pneumonia meta-analysis and analyzed only for the outcome of duration of hospitalization.

[e] The study was conducted with 3 groups with 30 people in each group (n = 90). The first group included multiple supplemental comprehensive oral care procedures (eg, lubrication of lips with vitamins A and D) and was excluded to ensure best comparability between the study arms among the included studies.

Figure 2. Risk of Bias Summary

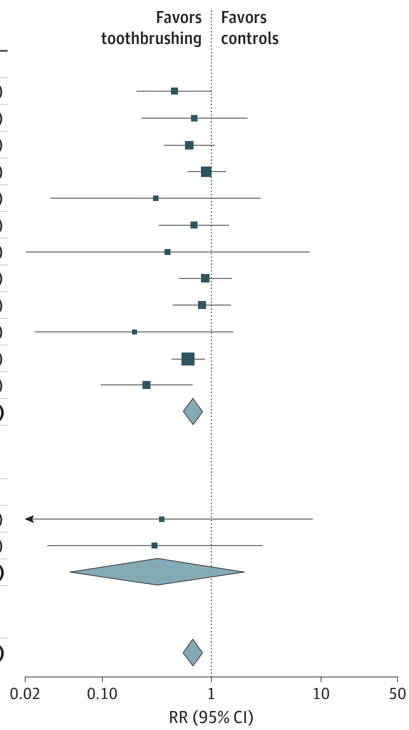


Green plus signs indicate low risk of bias; yellow question marks, unclear risk of bias; and red minus signs, high risk of bias.

[a] Salarzehi et al[32] and Falahinia et al[39] had a high risk of bias owing to convenience sampling. Giuliano et al[47] had an unclear risk of bias owing to industry supplying toothbrushing kits.

Figure 3. Association of Toothbrushing With Hospital-Acquired Pneumonia (HAP)

Source	Experimental group: No. of events	Experimental group: No. of patients	Control group: No. of events	Control group: No. of patients	RR (95% CI)	Weight, %
1.1.1 VAP						
Bellissimo-Rodrigues et al,[42] 2014	8	98	17	96	0.46 (0.21-1.02)	5.3
Chacko et al,[44] 2017	5	104	7	102	0.70 (0.23-2.14)	2.7
de Lacerda Vidal et al,[41] 2017	17	105	28	108	0.62 (0.36-1.07)	11.5
Falahinia et al,[39] 2016	19	34	21	34	0.90 (0.61-1.35)	21.0
Félix,[51] 2016	1	30	3	28	0.31 (0.03-2.82)	0.7
Gong et al,[31] 2018	9	40	13	40	0.69 (0.33-1.43)	6.3
Khan et al,[49] 2017	0	4	1	5	0.40 (0.02-7.82)	0.4
Lorente et al,[45] 2012	21	217	24	219	0.88 (0.51-1.54)	10.8
Pobo et al,[46] 2009	15	74	18	73	0.82 (0.45-1.50)	9.1
Salarzehi et al,[32] 2021	1	30	5	30	0.20 (0.02-1.61)	0.8
Singh et al,[43] 2022	32	110	52	110	0.62 (0.43-0.88)	26.9
Yao et al,[44] 2011	4	28	14	25	0.26 (0.10-0.67)	3.5
Subtotal	132	**874**	203	**870**	**0.68 (0.57-0.82)**	99.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{11} = 10.37$ ($P = .50$); $I^2 = 0\%$						
Test for overall effect: $z = 4.13$ ($P < .001$)						
1.1.2 NV-HAP						
Bellissimo-Rodrigues et al,[42] 2014	0	29	1	31	0.36 (0.02-8.39)	0.3
Giuliano et al,[47] 2021	1	393	3	360	0.31 (0.03-2.92)	0.7
Subtotal	1	**422**	4	**391**	**0.32 (0.05-2.02)**	1.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.01$ ($P = .94$); $I^2 = 0\%$						
Test for overall effect: $z = 1.21$ ($P = .23$)						
Total	133	**1296**	207	**1261**	**0.67 (0.56-0.81)**	100.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{13} = 11.01$ ($P = .61$); $I^2 = 0\%$						
Test for overall effect: $z = 4.23$ ($P < .001$)						
Test for subgroup differences: $\chi^2_1 = 0.63$ ($P = .43$); $I^2 = 0\%$						

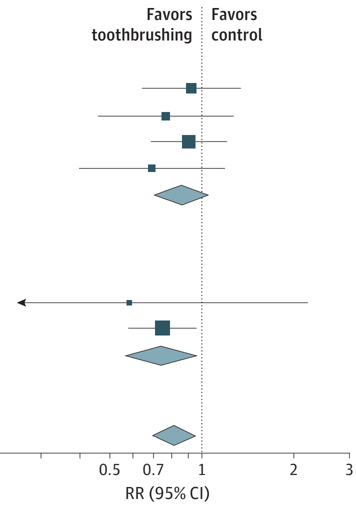


Data were synthesized using inverse-variance random-effects models, with effect sizes expressed as risk ratios (RR). NV-HAP indicates nonventilator HAP; VAP, ventilator-acquired pneumonia. Size of markers indicates the relative weight of each study within the meta-analysis.

[a] Reduced to effective sample sizes by calculating intraclass correlation and design effect according to the Cochrane Handbook.

Figure 4. Association of Toothbrushing With Intensive Care Unit Mortality

Source	Toothbrushing No. of events	Toothbrushing No. of patients	Control group No. of events	Control group No. of patients	RR (95% CI)	Weight, %
2.1.1 Low risk of bias						
Bellissimo-Rodrigues et al,[42] 2014	37	127	40	127	0.93 (0.64-1.34)	17.1
de Lacerda Vidal et al,[41] 2017	20	105	27	108	0.76 (0.46-1.27)	9.1
Lorente et al,[45] 2012	62	217	69	219	0.91 (0.68-1.21)	28.9
Pobo et al,[46] 2009	16	74	23	73	0.69 (0.40-1.19)	7.9
Subtotal	**135**	**523**	159	**527**	**0.86 (0.71-1.04)**	**63.0**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 1.14$ ($P = .77$); $I^2 = 0\%$						
Test for overall effect: $z = 1.54$ ($P = .12$)						
2.1.2 Unclear/high risk of bias						
Long et al,[50] 2012	3	31	5	30	0.58 (0.15-2.22)	1.3
Singh et al,[43] 2022	49	110	66	110	0.74 (0.57-0.96)	35.7
Subtotal	**52**	**141**	**71**	**140**	**0.74 (0.57-0.95)**	**37.0**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 12$ ($P = .72$); $I^2 = 0\%$						
Test for overall effect: $z = 2.37$ ($P = .02$)						
Total	**187**	**664**	**230**	**667**	**0.81 (0.69-0.95)**	**100.0**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 2.16$ ($P = .83$); $I^2 = 0\%$						
Test for overall effect: $z = 2.66$ ($P = .008$)						
Test for subgroup differences: $\chi^2_1 = 0.89$ ($P = .34$); $I^2 = 0\%$						



Data were synthesized using inverse-variance random-effects models, with effect sizes expressed as risk ratios (RR). Size of markers indicates the relative weight of each study within the meta-analysis.

Sensitivity analysis restricted to the 4 studies at low risk of bias yielded a similar effect estimate but broader 95% CIs that included 1.00 (RR, 0.86 [95% CI, 0.71-1.04]; I^2 = 0%).[41,42,45,46]

Duration of Mechanical Ventilation

Seven studies (n = 1285)[41-43,45,46,48,50] reported on duration of mechanical ventilation. Toothbrushing was associated with significantly less time to extubation (MD, −1.24 [95% CI, −2.42 to −0.06] days). On sensitivity analysis restricted to the 5 studies at low risk of bias,[41,42,45,46,48] the reduction in ventilated days remained significant (MD, −1.47 [95% CI, −2.57 to −0.36] days) and showed no heterogeneity (I^2 = 52% in the primary analysis vs I^2 = 0% in the sensitivity analysis).

ICU Length of Stay

Six studies (n = 1284) reported on ICU length of stay.[41-43,45,46,48] Toothbrushing was associated with significantly shorter ICU length of stay (MD, −1.78 [95% CI, −2.85 to −0.70] days; I^2 = 0%). Limiting to the 5 studies at low risk of bias,[41,42,45,46,48] toothbrushing remained associated with significantly shorter ICU length of stay (MD, −1.36 [95% CI, −2.58 to −0.14] days; I^2 = 0%).

Hospital Length of Stay

Two studies reported on duration of hospitalization (n = 921).[40,47] Both studies had a high or unclear risk of bias in multiple domains. One study included patients in the ICU receiving invasive mechanical ventilation,[40] while the other included patients in medical and surgical wards not receiving ventilation.[47] Neither study found an association with reduced hospital length of stay. These studies were not combined for meta-analysis because of the differences in their populations.

Antibiotic Use

Three studies reported on use of antibiotics (n = 667),[42,45,46] all based in the ICU and all at low risk of bias. Two studies[45,46] reported no significant difference in antibiotic-free days (RR, −0.52 [95% CI, −2.82 to 1.79]; I^2 = 0%), and 1 study[42] found no significant difference in total antibiotic days.

Subgroup Analysis

Two studies[42,51] had toothbrushing performed by dental professionals; in all other studies[31,32,39-41,43-50] oral care was performed by nondental nursing staff. One of the 2 studies in which toothbrushing was performed by dental professionals showed a significant reduction in HAP rates.[42] Two studies[46,48] used electric toothbrushes, one of which used electric and manual toothbrushes for cleaning. Only 1 of the 2 studies[48] showed an association with reduced HAP rates. Because of the small number of studies in these subgroups, meaningful subgroup analyses were not possible.

Certainty of the Evidence

Evaluating the certainty of evidence using the GRADE framework[34] and including only studies at low risk of bias, the quality of evidence for the reduction of pneumonia incidence is moderate due to risk of ascertainment bias for pneumonia, given the subjectivity of the diagnosis and the impossibility of blinding the individuals performing oral care. We also considered possible publication bias given visual asymmetry in the funnel plot (eFigure 1 in Supplement 1) but did not further downgrade the evidence because the Egger test result was not significant. For the outcomes of hospital length of stay and use of antibiotics, the strength of the recommendation was very low due to individual study limitations, imprecision, and possible publication bias.

Discussion

A systematic review and meta-analysis of 15 randomized trials showed that toothbrushing was associated with lower HAP rates, particularly in patients undergoing invasive mechanical ventilation, as well as lower ICU mortality rates, shorter ICU length of stay, and fewer days of mechanical ventilation. These findings suggest that routine toothbrushing should be considered an essential component of standard care in hospitalized patients, particularly in patients receiving invasive mechanical ventilation, for whom the evidence is strongest, to prevent pneumonia and lower mortality rates.

Our analysis helps clarify an effective oral care strategy for patients undergoing mechanical ventilation. Older guidelines and care improvement initiatives[61-63] recommended routine oral care with chlorhexidine for patients undergoing invasive mechanical ventilation. Subsequent analyses[19] questioned this recommendation, however, because of a possible association between oral care with chlorhexidine and higher mortality rates and uncertainty whether chlorhexidine truly lowers pneumonia rates. This led to a tempering or withdrawal of recommendations for oral chlorhexidine in subsequent guidelines, leaving frontline clinicians uncertain on whether and how best to provide oral care to prevent pneumonia. Our analysis helps clarify that toothbrushing may be an effective strategy to prevent VAP.

A strength of our study is that we examined patient-centered, objective outcomes in addition to pneumonia. This is important because pneumonia diagnostic criteria include subjective (eg, radiographic interpretation), nonspecific (eg, fever and abnormal white blood cell count), and variably sensitive (eg, positive culture yields) components.[52-59] These limitations of pneumonia diagnostic criteria complicate the interpretation of prevention studies and introduce risk of bias, particularly in open-label studies. Our findings were consistent, however, on sensitivity analysis restricted to studies in which the individuals assessing for pneumonia were blinded to patients' treatment assignments and in which there was no clear risk of bias in any other domain. Blinding outcomes assessment mitigates the risk of ascertainment bias due to the subjectivity of HAP diagnosis.[64-67] In addition, our finding that toothbrushing was associated with lower mortality rates, shorter duration of mechanical ventilation, and shorter ICU length of stay adds confidence that the observed association between toothbrushing and lower VAP rates was not spurious. The mortality signal was no longer significant in a sensitivity analysis restricted to studies at low risk of bias, but this may reflect diminished power, as the effect estimate was similar to the primary analysis (RRs, 0.86 [95% CI, 0.71-1.04] vs 0.81 [95% CI, 0.69-0.95]).

All but 1 study[47] in our analysis focused on patients in ICUs, most of whom received mechanical ventilation. Our findings are therefore strongest with regard to patients receiving invasive mechanical ventilation. We were only able to identify 2 studies with patients not receiving invasive mechanical ventilation that met inclusion criteria.[42,47] The effect estimates on combining these 2 studies was consistent with the primary analysis, but the sample size was small, the 95% CI was broad, and the signal was not statistically significant. This suggests that toothbrushing could also prevent NV-HAP, but more data are needed to confirm or refute this possibility.

Prior meta-analyses on the association between toothbrushing and VAP[20-24,26,29] have reported mixed results. Older meta-analyses[22-24,26] reported no association between toothbrushing and lower pneumonia rates, while more recent studies[20,21,29] have reported a positive association with lower VAP rates, but not with lower mortality rates. Our analysis includes substantially more studies than prior analyses, thus providing a more comprehensive and better powered assessment. Our results echo the findings of multiple preintervention and postintervention studies that reported decreases in VAP rates after implementing oral care protocols to prevent VAP[68-70] and NV-HAP.[71]

Although toothbrushing is an everyday action, the rigor, intensity, and frequency of toothbrushing may affect its capacity to prevent pneumonia and improve other outcomes. We found no evidence that brushing 3 or more times a day confers additional benefit over brushing 2 times a day. Subgroup analyses of care provided by dental professionals vs nondental nursing staff and on the use of electric vs manual toothbrushes included very few studies, thus precluding clear insight into the relative benefits of these strategies. Other questions we were unable to answer due to lack of pertinent studies include whether the type of toothpaste or choice of toothbrushing fluid affects outcomes, whether including tongue cleaning in the procedure increases the effect, and whether there is an interaction between toothbrushing and selective digestive tract decontamination. Similarly, we did not have patient-level data to assess whether effects differed for patients with oral vs nasal vs tracheal intubations or whether these effects differed by age group.

Limitations

Our study has several limitations. First, lack of double blinding may have biased outcome assessments. Results were consistent, however, on subgroup analysis restricted to studies where assessors were blinded to treatment assignment. Additionally, decreases in pneumonia rates were paralleled by decreases in mortality and ICU length of stay, affirming a possible beneficial effect of toothbrushing. Second, duration of follow-up was short in some studies, potentially leading to underdetection of pneumonia. Results were consistent, however, in the 7 studies with low risk of bias and a minimum of 7 days of follow-up[41,42,44-46,48,51] and in 5 studies at low risk of bias that followed up patients through extubation or 28 days.[41,42,44,46,51] Third, a funnel plot showed asymmetry and thus possible publication bias. Fourth, very few studies included patients who were not receiving invasive mechanical ventilation and those not in the ICU, thus limiting confidence in the effect of toothbrushing in these populations. Fifth, studies were heterogeneous with regard to country, setting, nursing protocols, and adjunctive measures. None of the studies among patients receiving invasive mechanical ventilation was performed in the US. Sixth, toothbrushing may have been a proxy for additional measures to prevent aspiration insofar as randomizing patients to toothbrushing may have sensitized nurses to patients' aspiration risk, leading them to be more vigilant.

Conclusions

The findings of this systematic review and meta-analysis of 15 randomized clinical trials suggest that oral care with toothbrushing may be associated with lower HAP rates, particularly among patients receiving invasive mechanical ventilation, as well as lower ICU mortality, reduced duration of mechanical ventilation, and shorter ICU length of stay compared with routine oral care without toothbrushing. These findings suggest the importance of developing policies and programs to encourage daily toothbrushing in hospitalized patients, particularly those receiving mechanical ventilation.

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Acquisition, analysis, or interpretation of data: Both authors.
Drafting of the manuscript: Both authors.
Critical review of the manuscript for important intellectual content: Klompas.
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