Effectiveness of Intraoral Chlorhexidine Protocols in the Prevention of Ventilator-Associated Pneumonia: Meta-Analysis and Systematic Review

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BACKGROUND: Ventilator-associated pneumonia (VAP) is common in critical patients and related with increased morbidity and mortality. We conducted a systematic review and meta-analysis, with intention-to-treat analysis, of randomized controlled clinical trials that assessed the effectiveness of different intraoral chlorhexidine protocols for the prevention of VAP. METHODS: Search strategies were developed for the MEDLINE, EMBASE, and LILACS databases. MeSH terms were combined with Boolean operators and used to search the databases. Eligible studies were randomized controlled trials of mechanically ventilated subjects receiving oral care with chlorhexidine or standard oral care protocols consisting of or associated with the use of a placebo or no chemicals. Pooled estimates of the relative risk and corresponding 95% CIs were calculated with random effects models, and heterogeneity was assessed with the Cochran Q statistic and $I^2$. RESULTS: The 13 included studies provided data on 1,640 subjects that were randomly allocated to chlorhexidine ($n = 834$) or control ($n = 806$) treatments. A preliminary analysis revealed that oral application of chlorhexidine fails to promote a significant reduction in VAP incidence (relative risk 0.80, 95% CI 0.59–1.07, $I^2 = 45\%$). However, subgroup analyses showed that chlorhexidine prevents VAP development when used at 2% concentration (relative risk 0.53, 95% CI 0.31–0.91, $I^2 = 0\%$) or 4 times/d (relative risk 0.56, 95% CI 0.38–0.81, $I^2 = 0\%$). CONCLUSIONS: We found that oral care with chlorhexidine is effective in reducing VAP incidence in the adult population if administered at 2% concentration or 4 times/d. Key words: chlorhexidine; clinical protocols; ventilator-associated pneumonia; meta-analysis; infection; critical care.

Introduction

Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops $\geq 48$ h after endotracheal intubation and initiation of mechanical ventilation. VAP is the second most common nosocomial infection in ICUs and the first most common in patients receiving mechanical ventilation. The condition is associated with increases in length of hospitalization and ICU stay, morbidity, mortality, and health-care costs. Despite recent advances in diagnosis and treatment of VAP, it continues to be a medical problem of major importance, with an attributable mortality rate between 33 and 50%. Thus, preventive interventions are needed to limit its occurrence.
The development of VAP is related to microbial colonization of the normally sterile lower respiratory tract by microorganisms commonly found in the trachea, oropharynx, stomach, or small or large intestines. Although the main route of infection leading to lower respiratory tract infection remains unknown, the primary source of infection for VAP is thought to be the oropharyngeal tract. Based on this, a significant number of studies have investigated the effect of topical oral antiseptics in VAP prevention. Among these antiseptics, chlorhexidine gluconate has attracted considerable attention, as evidenced by numerous randomized controlled clinical trials that have investigated the effect of oral chlorhexidine use in VAP prevention.

Results from the aforementioned randomized controlled trials and meta-analyses that analyzed the effect of oral care with chlorhexidine on VAP prevention are conflicting. Discrepant findings may have resulted from differences in study populations, diagnostic criteria for VAP, chlorhexidine concentration, and frequency of use. Meta-analyses have not reported the impact of specific protocols of oral care with chlorhexidine on VAP prevention. Moreover, previous meta-analysis mixed together outcomes reported on intention-to-treat and per-protocol basis. Therefore, in this paper, a systematic review and meta-analysis, with intention-to-treat analysis, of randomized controlled clinical trials was conducted to determine the effectiveness of oral decontamination with chlorhexidine and to compare specific protocols of oral care with chlorhexidine in VAP prevention.

Methods

Focused Question

We conducted a systematic review of the literature to assess the following focused PICO (patient or population, intervention, control or comparator, and outcome) question: In subjects endotracheally intubated and mechanically ventilated, does oral decontamination with chlorhexidine prevent the development of VAP, when compared with placebo or standard care or no treatment? As a second aim, this systematic review assessed the question: Which dose, frequency, or mode of use provides the best effect in the prevention of VAP? This systematic review was reported according to the PRISMA statement guidelines.

Eligibility Criteria

Type of Studies. Only randomized controlled trials that reported data using an intention-to-treat approach or provided enough information that per-protocol results could be adjusted into an intention-to-treat format were eligible for this review.

Type of Intervention and Comparison.

Exclusion Criteria

Search Strategy

Search strategies were developed for the MEDLINE, EMBASE, and LILACS databases. MeSH terms and key words were combined with Boolean operators and used to search the databases. All searches were done without language restriction, up to January 2015. The following terms were used: ([chlorhexidine OR “gluconate chlorhexidine” OR “oral decontamination” OR “oral hygiene” OR anti-septics OR “antiseptic decontamination”]) AND (“ventilator-associated pneumonia” OR VAP OR “nosocomial pneumonia” OR pneumonia OR intubation OR “mechanical ventilation” OR “intensive care units” OR “critical care”) AND (“clinical trial” OR RCT OR “randomized controlled trial” OR “randomized controlled clinical trial”). Electronic search was complemented by manual searches of the reference lists of selected full articles.

Outcome Measures. The primary outcome was incidence of VAP, reported as the number/percentage of affected subjects.

Study Population. The population of interest included intubated subjects receiving mechanical ventilation.

Current knowledge

In recent years, many regimens of oral care with chlorhexidine have been used on mechanically ventilated patients to prevent the development of ventilator-associated pneumonia (VAP). However, results from randomized controlled trials and meta-analysis that analyzed the effect of oral care with chlorhexidine on VAP prevention are still conflicting.

What this paper contributes to our knowledge

Results from this systematic review and meta-analysis indicate that oral care with chlorhexidine is effective in reducing VAP incidence only in the adult population and if administered at a 2% concentration or 4 times/d.
Screening Methods and Data Extraction

Two calibrated reviewers (DMN and CCV) independently screened titles and abstracts. Studies appearing to meet the inclusion criteria or those with insufficient information in the title and abstract to make a clear decision, were selected for full manuscript evaluation, which was carried out independently by the same 2 reviewers to determine study eligibility. Any disagreement was solved by discussion with a third reviewer (CMP). Reference lists of previous reviews and included studies were hand-searched. Studies that met the inclusion criteria underwent a validity assessment. Reasons for rejecting studies were recorded. Agreement between reviewers was described by kappa coefficient. Data were extracted independently by the same reviewers.

The following data were extracted and recorded: citation, setting and location of the trial, characteristics of participants, characteristics of the intervention (concentration, dose, frequency, and type of application), sample size, definition of VAP, and length of follow-up.

Quality Assessment and Data Synthesis

Quality assessment of the included studies was performed independently by 2 reviewers (DMN and CCV), with disagreements resolved by a third adjudicator (CMP). The following 6 domains were assessed as having low risk, high risk, or unclear risk of bias, according to the Cochrane Collaboration’s tool for assessing risk of bias.32

Then studies were categorized as follows: (1) low risk of bias, if all domains were met; (2) unclear risk of bias, if one or more domains were classified as having unclear risk of bias; and (3) “high risk” of bias, if one or more domains were not met.

Data Analysis

Analyses were performed using Review Manager 5.3 software (Cochrane Information Management System). Data on the incidence of VAP was extracted as dichotomous variables. Pooled estimates of the relative risk and the corresponding 95% CI were calculated using random effects models. Subgroup statistical heterogeneity among the studies was assessed with the Cochran Q statistic and I².

Results

The computerized search strategy yielded 211 citations, of which 53 were screened for potentially meeting the inclusion criteria (Fig. 1). Independent screening of abstracts led to the rejection of 30 articles (Fig. 1). The full text of the remaining 23 publications was obtained for review and possible inclusion. Scanning of reference lists yielded one additional study (Fig. 1). Of the 24 publications preselected, 9 articles were further excluded for reasons indicated in Figure 1. As a result, 13 studies published in English between September 2000 and November 2012 were included in this meta-analysis. The characteristics of the final trials retained are reported in Table 1.

Subject Selection and Characteristics

The 13 included studies provided data on 1,640 subjects who were randomly allocated to chlorhexidine (n = 834) or control (n = 806) treatments. Studies enrolled subjects expected to require orotracheal or nasotracheal intubation and mechanical ventilation.8-10,12,14,15,17-19,21,22,24,25 Among these, some studies required mechanical ventilation for at least 48 h.10,12,22,24 Other studies only included subjects with medical conditions suggesting an ICU stay of ≥48 h,15 3 d,18 or 5 d8,9 (Table 1). In 3 studies, research subjects...
### Table 1. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Subject Source</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Diagnostic Information</th>
<th>Experimental Group</th>
<th>Control Group</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geer et al (2004)</td>
<td>Surgical, trauma and neuroscience ICU and Emergency Department, United States</td>
<td>Age ≥ 18 y, endotracheally intubated and mechanically ventilated for 48 h</td>
<td>Edentulous subjects</td>
<td>CPIS ≥6</td>
<td>CHX 0.12% solution; single full-mouth application delivered as 20 sprays (n = 5) or by swabbing (n = 2) at early post-intubation period</td>
<td>Standard oral care (n = 5)</td>
<td>Subjects were followed for 72 h after intubation or until extubation if extubated before 72 h</td>
</tr>
<tr>
<td>Fourrier et al (2005)</td>
<td>6 ICUs (3 in university hospitals and 3 in general hospitals); France</td>
<td>Age &gt; 18 y, medical condition suggesting ICU stay ≥5 d and requiring mechanical ventilation by orotracheal or nasotracheal intubation; only subjects hospitalized for &lt;48 h before ICU admission were included</td>
<td>Edentulous subjects, subjects with a tracheostomy tube, facial trauma, post-surgical and requiring specific oropharyngeal care, allergy to CHX</td>
<td>Temperature &gt;38°C or &lt;36°C or infiltrates on chest radiographs, leukocytosis (&gt;10 × 10⁹/mm³) or leukopenia (&lt;3 × 10⁹/mm³), positive quantitative culture of tracheal aspirate (≥10⁴ CFU/mL) and/or bronchoalveolar lavage fluid (≥10² CFU/mL)</td>
<td>CHX 0.2% gel (n = 114); applied over dental and gingival surfaces by nurses wearing sterile gloves, after mouth rinsing and oropharyngeal aspiration; gel was left in place, and the oral cavity was not rinsed after application; CHX application started within the first 24 h of intubation; intervention was performed at least 3 times/d until day 28, discharge, or death; tooth brushing was not allowed</td>
<td>Placebo gel (n = 114); applied according to the same oral care protocol used in the experimental group</td>
<td>Entire ICU stay</td>
</tr>
<tr>
<td>Koeman et al (2006)</td>
<td>5 mixed and 2 surgical ICUs; Netherlands</td>
<td>Age &gt; 18 y, requiring mechanical ventilation for ≥48 h, included within 24 h after intubation and start of mechanical ventilation</td>
<td>Preadmission immunocompromised status, pregnancy, physical condition not allowing oral application of study medication</td>
<td>New, persistent, or progressive infiltrate on chest radiographs, in combination with at least 3 of 4 criteria: body temperature &gt;38°C or &lt;35.5°C, blood leukocytosis (&gt;10 × 10⁹/mm³), and/or left shift or leukopenia (&lt;3 × 10⁹/mm³), purulent aspect of tracheal aspirate, and a positive semiquantitative culture from tracheal aspirates (≥10⁴ CFU/mL) after 48 h of mechanical ventilation</td>
<td>CHX 2% in Vaseline petroleum jelly (n = 127); 2 cm of paste (0.5 g) put on a gloved fingertip and administered to each side of the buccal cavity, after removing remnants of the previous dose with a saline moistened gauze; intervention was performed 4 times/d, until VAP diagnosis, death, extubation, or withdrawal; CHX 2%/colistin in Vaseline petroleum jelly (n = 128) used according to the protocol described above</td>
<td>Vaseline petroleum jelly (n = 150); applied according to the same oral care protocol used in the experimental groups</td>
<td>Subjects were followed until extubation, death, development of pneumonia, or withdrawal of consent</td>
</tr>
<tr>
<td>Tantipong et al (2008)</td>
<td>Tertiary care, ICUs, or general medical wards; Thailand</td>
<td>Age ≥18 y, requiring mechanical ventilation</td>
<td>Pneumonia at enrollment, allergy to CHX</td>
<td>New, persistent, or progressive infiltrate on chest radiograph, in combination with at least 3 of the following 4 criteria: body temperature &gt;38°C or &lt;35.5°C, leukocytosis (&gt;10 × 10⁹ leukocytes/mm³) or leukopenia (&lt;3 × 10⁹ leukocytes/mm³), purulent tracheal aspirate, and/or a positive semiquantitative culture of tracheal aspirate samples for pathogenic bacteria</td>
<td>CHX 2% solution (n = 102); oral care consisted of tooth brushing, suctioning of oral secretions, and rubbing the oropharyngeal mucosa with 15 mL of CHX; intervention was performed 4 times/d until removal of the endotracheal tube</td>
<td>Normal saline solution (n = 105); applied according to the same oral care protocol used in the experimental group</td>
<td>Subjects were followed until extubation or development of pneumonia</td>
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<tr>
<td>Bellissimo-Rodrigues et al (2009)</td>
<td>Clinical and surgical ICU; Brazil</td>
<td>Expected ICU stay ≥ 48 h, included within 24 h after ICU admission, regardless of whether receiving mechanical ventilation; tracheotomized subjects were included</td>
<td>CHX hypersensitivity, pregnancy, formal indication for CHX use, or prescription of another oral topical medication</td>
<td>According to the criteria defined by the CDC and NNIS system</td>
<td>CHX 0.12% solution (total n = 98, on mechanical ventilation n = 64); after mechanical cleaning of the mouth by nurses, 15 mL was applied over all surfaces of the oral cavity; intervention was performed 3 times/d until ICU discharge</td>
<td>Placebo solution (total n = 96, on mechanical ventilation n = 69), applied according to the same oral care protocol used in the experimental group</td>
<td>Entire ICU stay</td>
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<tr>
<td>Scannapieco et al (2009)</td>
<td>Trauma ICU; United States</td>
<td>Subjects expected to be intubated and mechanically ventilated within 48 h of ICU admission</td>
<td>Witnessed aspiration, confirmed diagnosis of post-obstructive pneumonia, hypersensitivity to CHX, thrombocytopenia, a “do not intubate” order, age &lt; 18 y, pregnancy, legal incarceration, transfer from another ICU, oralmucositis, immunosuppression, readmission to the ICU</td>
<td>CPIS ≥ 6 associated with the presence of ≥ 10^5 CFU/mL of a target putative respiratory pathogen in bronchoalveolar lavage fluid or a positive pleural fluid culture in the absence of previous pleural instrumentation</td>
<td>CHX 0.12% alcoholic solution (n = 58); 1 ounce applied using an oral foam applicator over all teeth and intra-oral soft tissues and suctioned after 1 min (2 times/d) + tooth brushing with a suction toothbrush (2 times/d) + swabbing with 1.5% hydrogen peroxide solution (6 times/d) + application of a mouth moisturizer; CHX 0.12% (n = 58); oral care protocol identical to the one described above, except that CHX was applied only 1 time/d</td>
<td>Placebo (n = 59); 1 ounce applied using an oral foam applicator over all teeth and intra-oral soft tissues and suctioned after 1 min (2 times/d) + tooth brushing with a suction toothbrush (2 times/d) + swabbing with Peroxamint solution (6 times/d) + application of a mouth moisturizer to the oral mucosa</td>
<td>Placebo were followed for up to 21 d or until discharge from ICU, extubation, or death</td>
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<tr>
<td>Cabov et al (2010)</td>
<td>Surgical ICU; Croatia</td>
<td>Age &gt; 18 y, medical condition suggesting ICU stay ≥ 3 d, eventual requirement for mechanical ventilation by orotracheal or nasotracheal intubation</td>
<td>Edentulous subjects</td>
<td>Temperature &gt; 38°C or &lt; 36°C, infiltrates on chest radiographs, leukocytosis (&gt; 10^9/L) or leukopenia (&lt; 3 x 10^9/L/mm³), positive culture from tracheal aspirate and/or bronchoalveolar lavage</td>
<td>CHX 0.2% gel (total n = 30, without a diagnosis of pneumonia at baseline n = 17); applied over dental and gingival surfaces by nurses wearing sterile gloves, after mouth rinsing with bicarbonate isotonic serum followed by oropharyngeal aspiration; gel was left in place, and the oral cavity was not rinsed after application; CHX application started early after intubation; intervention was performed 3 times/d during ICU stay</td>
<td>Placebo gel (total n = 30, without a diagnosis of pneumonia at baseline n = 23); applied according to the same oral care protocol used in the experimental group</td>
<td>Until ICU discharge or death</td>
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Table 1. Continued

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<tbody>
<tr>
<td>Berry et al (2011)39</td>
<td>Surgical-medical ICU; United States</td>
<td>Age ≥15 years, intubated and able to be randomized within 12 h of intubation</td>
<td>Subjects who required specific oral hygiene procedures in relation to faceo-maxillary or dental trauma/surgery; had been in the ICU previously during the current period of hospitalization; received irradiation or chemotherapy on admission to the ICU or in the preceding 6 wks; or suffered from autoimmune diseases</td>
<td>New or worsening radiological infiltrates, together with ≥2 of the following: temperature ≥37.5°C or &lt;35°C; white cell count &gt;11,000/mm³ or &lt;4,000/mm³; change in characteristics of bronchial secretions from mucoid to mucus-purulent or purulent; increase in fraction of inspired oxygen or positive end-expiratory pressure requirement by ≥20% to maintain oxygen saturation above 92%</td>
<td>CHX 0.2% aqueous solution (n = 71); irrigation with CHX (2 times/d), with second hourly irrigation with sterile water and comprehensive cleaning of the mouth using a soft, pediatric toothbrush (3 times/d); Control I (n = 78): sterile water rinsed second hourly and comprehensive cleaning of the mouth using a soft, pediatric toothbrush 3 times/d</td>
<td>Control II (n = 76): sodium bicarbonate mouthwash rinsed second hourly and comprehensive cleaning of the mouth using a soft, pediatric toothbrush 3 times/d</td>
<td>Protocol was followed until the patient was extubated or upon ICU discharge, tracheotomy, or death</td>
</tr>
<tr>
<td>Jácomo et al (2011)31</td>
<td>Tertiary care PICU; Brazil</td>
<td>Children with congenital heart disease undergoing cardiac surgery with or without cardiopulmonary bypass admitted to the PICU in the postoperative period</td>
<td>Subjects with a preoperative diagnosis of pneumonia, hypersensitivity to CHX, congenital or acquired immunodeficiency, intraoperative death, failure to perform oral hygiene perioperatively</td>
<td>According to the criteria defined by the CDC and NNIS system</td>
<td>CHX 0.12% alcoholic solution (n = 89); 0.3 ml of solution/kg of body weight was used preoperatively (before intubation), for 30 s, as an oral rinse in children &lt;6 y old; and during orotracheal intubation, the solution was applied to the oral mucosa, gingiva, tongue, and tooth surfaces over a period of 30 s with a spatula wrapped with gauze; intervention was performed 2 times/d postoperatively until PICU discharge or death</td>
<td>Placebo solution (n = 75), applied according to the same oral care protocol used in the experimental group</td>
<td>Subjects were followed until PICU discharge or death</td>
</tr>
<tr>
<td>Kasahara et al (2012)22</td>
<td>Tertiary care PICU; Brazil</td>
<td>Children likely to require intubation and mechanical ventilation within 24 h of PICU admission</td>
<td>Newborn status, diagnosis of pneumonia at admission, hypersensitivity to CHX, duration of mechanical ventilation &lt;48 h, children with tracheostomy or who received tracheal intubation for &gt;24 h before PICU admission</td>
<td>The development of VAP was quantified using CPIS and confirmed by the alternate pneumonia clinical criteria for infants and children, as defined by the CDC/National Healthcare Safety Network</td>
<td>CHX 0.12% gel (n = 46); gel was applied to a toothbrush, and all tooth surfaces and ventral surface of the tongue were cleaned and aspirated with a vacuum; next, the gel was applied by a swab over all gingival surfaces; intervention was performed 2 times/d, for up to 15 d or until death or extubation</td>
<td>Placebo gel (n = 50), applied according to the same oral care protocol used in the experimental group</td>
<td>Subjects were followed until they exited the study or were discharged from the hospital</td>
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<tr>
<td>Ozcaka et al (2012)24</td>
<td>Respiratory ICU; Turkey</td>
<td>Dentate subjects expected to be intubated and mechanically ventilated for ≥48 h after ICU admission</td>
<td>Witnessed aspiration, confirmed diagnosis of post-obstructive pneumonia, hypersensitivity to CHX, thrombocytopenia, a “do not intubate” order, age &lt;18 y, pregnancy, oral mucositis, readmission to the same ICU, survival expectation &lt;1 wk and edentulism</td>
<td>The presence of ≥104 CFU/mL of a target putative respiratory pathogen in mini-bronchoalveolar lavage fluid or a positive pleural fluid culture in the absence of previous pleural instrumentation</td>
<td>CHX 0.2% solution (n = 32); 30 mL applied by oral swab to all teeth and intra-oral soft tissues and suctioned after 1 min; intervention was performed 4 times/d, for up to 14 d or until discharge from ICU, extubation, or death</td>
<td>Saline solution (n = 34), applied according to the same oral care protocol used in the experimental group</td>
<td>Subjects were followed for up to 14 d or until ICU discharge, extubation, or death</td>
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</table>
Subjects were followed for a period of 21 days or until hospital discharge, whichever was earlier. Placebo gel (total n/H1105 45, n/H1109 16), applied without a diagnosis of pneumonia at baseline according to the same oral care protocol used in the experimental group and proofread. However, this version may differ from the final published version in the online and print editions of RESPIRATORY CARE.

In subjects with no evidence of preexisting pneumonia, diagnosis of VAP was made based on the criteria established by the CDC; in subjects with underlying pneumonia, worsening of clinical and radiological findings and changes in bronchoalveolar lavage fluid flora were used to diagnose VAP.

Table 1. Continued

<table>
<thead>
<tr>
<th>Study (Year)</th>
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<th>Inclusion Criteria</th>
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</tr>
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<tbody>
<tr>
<td>Sebastian et al (2012)</td>
<td>PICU; India</td>
<td>Age &lt; 3 mo and &lt; 15 y, requiring mechanical ventilation</td>
<td>No evidence of preexisting pneumonia, rash, or hypersensitivity to CHX</td>
<td>CHX 1% gel was applied to the buccal mucosa, after mouth aspiration and cleansing with saline-soaked gauze; intervention was performed 3 times/d, for up to 21 d</td>
<td>CHX 1% gel (total n/H1105 41, n/H1109 15); 0.5 g (1.5 cm) of gel was applied over the buccal mucosa, after mouth aspiration and cleansing with saline-soaked gauze; intervention was performed 3 times/d, for up to 21 d</td>
<td>Placebo gel (total n/H1105 45, n/H1109 16), applied without a diagnosis of pneumonia at baseline according to the same oral care protocol used in the experimental group</td>
<td>Subjects who had been mechanically ventilated for &gt; 24 h before PICU admission, with tracheostomies, within accessible oral cavities, hypersensitivity to CHX</td>
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</table>

Intraoral Chlorhexidine for Prevention of VAP

Included studies were also quite homogeneous in their intervention regimens. Among them, chlorhexidine was used at concentrations of 0.12%, 0.2%, 8,9,18,19,24 1%, 23 and 2%,12,14 (Table 1). Chlorhexidine was applied as oral rinse solution, 10,14,15,19,21,24 gel, 8,9,18,22,25 Vaseline petroleum jelly, 12 and foam 17 (Table 1). When specified by the authors, chlorhexidine solutions were reported as aqueous 19 or alcoholic. 17,21

The frequency of chlorhexidine oral application also varied among the studies. Chlorhexidine was used in a single dose at intubation, 10 once/d, 17 twice/d, 17,19,21,22 3 times/d, 8,9,15,18,25 or 4 times/d 12,14,24 (Table 1).

Methodological Quality of the Studies

Studies’ individual risk of bias were assessed and listed in Table 2. Details related to the method of randomization were provided in all studies.8-10,12,14,15,17-19,21,22,24,25 Allocation concealment was adequately described only in 4 studies.8,15,17,21 Moreover, one study 25 reported that allocation was concealed but did not provide details of the concealment. The remaining 8 studies did not provide any information about allocation concealment.9,10,12,14,18,19,22,24

Whereas study subjects and personnel were blinded in only 8 trials, 8,12,15,17,18,21,22,25 outcome assessors were blinded in all studies.8-10,12,14,15,17-19,21,22,24,25

Incomplete outcome data were adequately addressed in 5 studies.12,15,21,24,25 In 3 studies,9,17,18 the reasons for missing data in each group were not provided. In 2 others, the dropout rate was significantly higher in the chlorhexidine group.10,19 In Fourrier et al,9 the proportion of missing outcomes compared with observed event risk was high enough to induce relevant bias. Finally, the reasons for missing outcomes were likely to be related to the true outcome in Kusahara et al.22

Sample size calculation was not described in 4 studies,9,10,18,22 Moreover, in the other 4, final sample size was smaller than the number indicated by sample size calculations.8,14,19,25
### Table 2. Risk of Bias

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Participants and Personnel</th>
<th>Blinding of Outcome Assessor</th>
<th>Incomplete Outcome Data</th>
<th>Selective Reporting</th>
<th>Other Sources of Bias</th>
<th>Overall Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fourrier et al (2000)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Gop et al (2004)</td>
<td>Low (Subjects were randomized into two groups according to computer-generated randomization table)</td>
<td>Low (Subjects were randomized into two groups by spraying or swab to the oropharynx and nasopharynx)</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Fourrier et al (2005)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
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<tr>
<td>Scannapieco et al (2009)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Cabov et al (2010)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Low</td>
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<tbody>
<tr>
<td>Berry et al (2011)</td>
<td>Low (Subjects were randomized into one of three groups according to a balanced randomization table prepared by a biostatistician)</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>High (percentage of missing outcome data was smaller in number in the placebo group; frequency of protocol breach was higher in the treatment groups; frequency of subject death was higher in the sodium bicarbonate group)</td>
<td>Low</td>
<td>High (number of subjects was smaller than the one defined by the sample size calculation)</td>
<td>High</td>
</tr>
<tr>
<td>Jácomo et al (2011)</td>
<td>Low (Subjects were randomized to the experimental or the control group by means of a list generated by a computerized system that uses a random number generator to produce customized sets of random numbers)</td>
<td>Low (The randomization list was held in the hospital pharmacy, and all investigators were unaware of subjects’ assignments)</td>
<td>Low</td>
<td>Low</td>
<td>Low (percentage of missing outcome data was balanced in number across intervention groups, with similar reasons for missing data across groups)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Kusuhara et al (2012)</td>
<td>Low (Children were sequentially randomized into two groups using a balanced randomization table generated by the True Epistat program)</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>High (reason for the missing outcome data likely to be related to the true outcome)</td>
<td>Low</td>
<td>High (age difference, no sample size calculation)</td>
<td>High</td>
</tr>
<tr>
<td>Özçaka et al (2012)</td>
<td>Low (The randomization prepared a set of subject identification numbers (SIDs) that identified individual treatment assignments)</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low (percentage of missing outcome data was balanced in number across intervention groups, with similar reasons for missing data across groups)</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sebastian et al (2012)</td>
<td>Low (The random sequence was generated for each stratum using the STATA 9.0 program in blocks of 6)</td>
<td>Low (Randomization and numbering of the tubes were done by personnel not involved in the study, and the allocation sequence remained concealed through the entire length of the study)</td>
<td>Low</td>
<td>Low</td>
<td>Low (percentage of missing outcome data was balanced in number across intervention groups, with similar reasons for missing data across groups)</td>
<td>Low</td>
<td>High (number of subjects randomized was smaller than the number suggested by the sample size calculation)</td>
<td>High</td>
</tr>
</tbody>
</table>

CHX = chlorhexidine
VAP = ventilator-associated pneumonia
Effect of Oral Care With Chlorhexidine on VAP Prevention

A preliminary analysis including 1,640 pediatric and adult subjects revealed that oral application of chlorhexidine did not promote a significant reduction in VAP incidence (relative risk 0.80, 95% CI 0.59–1.07, $I^2 = 45\%$) (Fig. 2). Next, subgroup analyses were conducted to compare the effect of chlorhexidine in pediatric and adult populations. Similar to the results found in the overall study population, oral care with chlorhexidine failed to prevent VAP in the pediatric population (relative risk 1.13, 95% CI 0.76–1.67, $I^2 = 0\%$) (see Fig. 2). Nonetheless, oral application of chlorhexidine promoted a trend toward a protective effect in adult subjects (relative risk 0.70, 95% CI 0.48–1.00, $I^2 = 47\%$) (see Fig. 2). Due to the limited number of studies that investigated the effect of oral care with chlorhexidine on VAP prevention in pediatric subjects and the lack of effects of oral care with chlorhexidine in this study population, the following subgroup analyses were conducted based on adult population data only.

Effect of Chlorhexidine Concentration

Subgroup analysis investigated chlorhexidine used in concentrations of 0.12, 0.2, and 2% (Fig. 3). At the lowest concentrations tested (0.12 and 0.2%), chlorhexidine failed to prevent VAP development (0.12% chlorhexidine: relative risk 1.00, 95% CI 0.51–1.99, $I^2 = 54\%$; 0.2% chlorhexidine: relative risk 0.63, 95% CI 0.32–1.22, $I^2 = 57\%$). In sharp contrast, 2% chlorhexidine promoted a significant reduction in VAP incidence (relative risk 0.53, 95% CI 0.31–0.91, $I^2 = 0\%$).

Effect of Chlorhexidine Frequency of Use

Subgroup analyses investigated chlorhexidine used in a single application at intubation and once, twice, 3 times, or 4 times daily (Fig. 4). When used as a single application dose at intubation, in the study published by Grap et al., chlorhexidine failed to reduce the incidence of VAP (relative risk 2.79, 95% CI 0.75–10.37). Likewise, chlorhexidine used at frequencies of once/d, twice/d, and 3 times/d also failed to prevent VAP development (once/d: relative risk 0.59, 95% CI 0.25–1.40; twice/d: relative risk 1.25, 95% CI 0.19–8.31, $I^2 = 65\%$; 3 times/d: relative risk 0.64, 95% CI 0.31–1.31, $I^2 = 62\%$). The protective effect of chlorhexidine was only achieved when its frequency of use was increased to 4 times/d (relative risk 0.56, 95% CI 0.38–0.81, $I^2 = 0\%$).
Effect of Chlorhexidine Used as Monotherapy or in Combination With Mechanical Means

In some studies, chlorhexidine was the only form of oral care.8–10,12,18,24 On the contrary, in some others, chlorhexidine was associated with mechanical debridement.14,15,17,19 Therefore, an analysis was undertaken to assess the effectiveness of chlorhexidine used alone and in association with mechanical means for the prevention of VAP (Fig. 5). Used as monotherapy, chlorhexidine failed to reduce VAP incidence (relative risk 0.65, 95% CI 0.39–1.09, I² = 55%). Similarly, chlorhexidine did not promote a significant reduction in VAP incidence when used in conjunction with mechanical cleansing of the oral cavity (relative risk 0.77, 95% CI 0.43–1.39, I² = 42%).

Safety

Six studies reported that the oral use of chlorhexidine was associated with no adverse effects.15,17,19,21,24,25 Another 6 studies failed to provide information about its safety.8–10,12,18,22 One study reported that mild and reversible irritation of the oral mucosa was more common in subjects treated with chlorhexidine 2% solution than in those treated with normal saline.14

Discussion

With an intention-to-treat analysis, the present meta-analysis provides the most comprehensive assessment to date of the effect of different protocols of oral care with chlorhexidine in VAP prevention in a non-cardiac surgery population. According to our results, the effectiveness of oral care with chlorhexidine in VAP prevention is influenced by the age of the population and the concentration and frequency of application of chlorhexidine.

The current study demonstrated that oral care with chlorhexidine promoted a trend toward VAP prevention in adult subjects but failed to prevent disease development in newborns and infants. There are 3 possible explanations for this discrepancy. First, it is plausible that the antimicrobial effects of chlorhexidine cannot overcome the relative immaturity of the immune system of newborns and infants. The relevance of newborn respiratory innate immunity to the pathogenesis of respiratory diseases in newborns and infants is beginning to surface. Plasmatic levels of complement components and other multifunctional soluble immune proteins are significantly lower in newborns compared with adults.33 Moreover, existing evidence based on animal models indicates that a post-natal impairment of TLR2 and TLR4 expression negatively affects inflammatory responses following intratracheal administration of
Gram-negative bacteria early in life. Likewise, a strong bias against T helper cell type 1 polarization of the immune response is also thought to make infants more susceptible to microbial infections. Second, it is reasonable to speculate that the small oral cavity associated with the relatively large tongue in newborns and infants is likely to pose technical difficulties in providing proper oral care with chlorhexidine to these subjects. Last, the lack of chlorhexidine effect in the pediatric population might be simply explained by the fact that none of the pediatric trials used 2% formulations or rendered oral decontamination with chlorhexidine 4 times/d.

This meta-analysis demonstrated that the effectiveness of oral care with chlorhexidine on prevention of VAP is dose- and frequency-dependent. Subgroup analysis demonstrated that 0.12 and 0.2% chlorhexidine failed to promote a significant reduction in VAP incidence in adult subjects. In sharp contrast, 2% chlorhexidine promoted a significant reduction in the incidence of VAP, with a relative risk of 0.53. Two previous meta-analyses showed similar results, with a relative risk of 0.53 for chlorhexidine 2%. The antibacterial activity of chlorhexidine is dose-dependent. Higher and longer lasting antimicrobial activity has been reported for 2% chlorhexidine as compared with less concentrated formulations, which could explain the superior results of oral care with 2% chlorhexidine in VAP prevention. Nonetheless, it is important to note that data about the tolerance of 2% solutions were provided by only one study that reported mild and reversible irritation of the oral mucosa with the use of...
2% chlorhexidine solution.\textsuperscript{1,4} Moreover, 2% chlorhexidine solutions are not available worldwide and are often only made for study purposes. This study showed for the first time that oral care with chlorhexidine is only effective in reducing VAP incidence when provided 4 times/d. Numerous authors have demonstrated the immediate antibacterial effect of chlorhexidine and the persistence of its substantivity for up to 12–14 h after its administration. However, the clinical relevance of this information has been challenged, since rising evidence suggests that although chlorhexidine can be found in the oral cavity for \textsuperscript{1/2}12 h, its antimicrobial activity lasts only 7 h after a mouth rinse.\textsuperscript{37,38} Thus, it is likely that the effectiveness of oral care with chlorhexidine in VAP prevention is dependent on its persistent antimicrobial activity.

Along these lines, 2% chlorhexidine was used in only 2 of the total of 10 adult population trials included in this meta-analysis. On a patient level, this signifies that only 33% of subjects receiving oral care with chlorhexidine were treated with the 2% formulation. Chlorhexidine was administered 4 times/d in only 3 trials included in this meta-analysis, encompassing only 38% of subjects receiving oral care with chlorhexidine. As previously mentioned, the current study showed that oral care with chlorhexidine promoted only a trend toward VAP prevention in adult subjects. Thus, it is reasonable to speculate that the overall effect of oral care with chlorhexidine in VAP prevention could have been stronger if more trials had administered chlorhexidine at 2% or rendered treatment 4 times/d. Also, the wide variety of combinations of chlorhexidine concentrations and dose intervals reported in studies included in this meta-analysis have precluded the investigation of potential interplays of chlorhexidine concentration and frequency of use in VAP prevention. A ventilator bundle is a group of interventions related to ventilator care that, when implemented together, promotes significantly better outcomes. The VAP prevention bundle is a widely used ICU protocol that includes elevation of the head of the bed, daily sedation vacations and assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep vein thrombosis prophylaxis, and oral decontamination with chlorhexidine. Thus, it is also plausible that oral decontamination with chlorhexidine failed to promote an overall significant reduction in VAP incidence because other bundle prevention measures had been successfully implemented and limited VAP development.

Subanalyses conducted to specifically assess the effectiveness of oral chlorhexidine used alone and in association with mechanical means in the prevention of VAP showed that none of these protocols were able to reduce VAP incidence. These results, however, must be interpreted cautiously due to the large methodological heterogeneity across the limited number of studies included in this subanalysis. The observation that oral chlorhexidine alone might be slightly superior due to its association with mechanical means for VAP prevention is likely to be misleading. First, no direct comparison was made between these protocols. Second, the meta-analysis that assessed the efficacy of chlorhexidine associated with mechanical means included fewer subjects receiving 2% chlorhexidine and/or rendered treatment 4 times/d than the meta-analysis...
of studies assessing the efficacy of chlorhexidine alone. Of interest, a meta-analysis of 4 low-quality trials found no difference between oral care with chlorhexidine plus tooth brushing and oral care with chlorhexidine alone in terms of VAP prevention.28

Finally, only 2 studies included in this meta-analysis reported the periodontal conditions of enrolled subjects.17,24 Potential associations between periodontal disease and periodontal disease-associated micro-organisms and the development of nosocomial pneumonia have been already proposed.40 Thus, it is plausible to speculate that oral care with chlorhexidine is more likely to prevent VAP development in subjects with periodontal infection.

Conclusions

We found that oral care with chlorhexidine is effective in reducing VAP incidence in the adult population only if chlorhexidine is administered at 2% or 4 times/d. These findings, however, must be interpreted cautiously, due to the high heterogeneity of the studies and small number of trials that tested the safety and effectiveness of chlorhexidine at 2% or rendered treatment 4 times/d. Further investigation of intervention protocols implementing oral chlorhexidine at high concentration and frequency to reduce VAP in subjects with a known periodontal status is required before definitive recommendations can be made.

REFERENCES

INTRAORAL CHLORHEXIDINE FOR PREVENTION OF VAP