Oral chlorhexidine in the prevention of ventilator-associated pneumonia in critically ill adults in the ICU: A systematic review

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Purpose. The aim of this review was to evaluate the evidence on the effectiveness of oral chlorhexidine in the prevention of ventilator-associated pneumonia (VAP) in critically ill adult mechanically ventilated patients in intensive care units (ICUs).

Methodology. An extensive literature search of studies published in English was undertaken between June 2010 and June 2011. Electronic databases searched were the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index of Nursing and Allied Health (CINAHL) and MEDLINE. Reference lists of articles, textbooks and conference summaries were examined and hand searching was performed. Literature searches were done using the following Medical Subject Headings (MeSH) terms: ventilator-associated pneumonia, VAP, chlorhexidine, hospital-acquired pneumonia, nosocomial infections, mechanically ventilated patients, intensive care, mouthwash, mouth care, oral care, oral hygiene and dental care.

Selection criteria. Two reviewers selected the studies independently. Eight randomised controlled trials investigating the efficacy of oral chlorhexidine versus power tooth brushing, Listerine, placebos, bicarbonate isotonic serum rinse and normal saline in the prevention of VAP in adult mechanically ventilated, critically ill patients in ICUs met the inclusion criteria.

Data collection and analysis. All relevant data were entered into Review Manager (version 5.1) for analyses. The effect measure of choice was the risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous data using the random effects (Mantel-Haenszel) model (p-value 0.05). Heterogeneity was assessed using the Cochrane Q statistic and I².

Results. Eight randomised controlled trials met the inclusion criteria for this review. There was a 36% higher chance of VAP in the control group compared with the chlorhexidine group (RR 0.64, 95% CI 0.44 - 0.91). The variation between the included studies was very small (χ²=0.24).

Conclusion. Treatment with chlorhexidine decreased the risk of VAP by 36%. The use of 2% chlorhexidine may be most effective in reducing the incidence of VAP. There was no evidence of an effect of chlorhexidine on mortality.

Between 9% and 27% of patients who are mechanically ventilated will develop ventilator-associated pneumonia (VAP). Mortality rates for patients who develop VAP are high, with 33 - 50% of ventilated patients dying.¹ No statistical data on nosocomial infections or nosocomial pneumonia relevant to South Africa or developing countries were found in an extensive literature search.

Description of the condition
VAP can occur in critically ill patients who are mechanically ventilated for periods longer than 48 hours.² Pathogenesis involves the entry of bacteria to the patient's lower respiratory tract and overwhelming of the patient's defences.³

VAP can be identified when a chest radiograph shows a new or progressive infiltrate, consolidation, cavitations or pleural effusions and the patient has at least one of the following symptoms: new onset of purulent sputum or a change in colour of sputum, increased temperature, increased or decreased white cell count, organisms cultured from blood, and isolation of an aetiological agent by transtracheal aspirate, bronchial brushing or biopsy.⁴ Mechanical ventilation is used as support therapy in approximately one-third of patients in intensive care units (ICUs).⁵

How chlorhexidine might work
Sequential sampling of dental plaque from ICU patients showed that more than 50% of those who acquire a respiratory infection have been colonised earlier by the same pathogens at the gingivodental level.⁶ Teeth should be considered a substantial reservoir for respiratory pathogens, and decontamination of the oropharynx with antiseptic solutions could reduce the incidence of acquired respiratory infections.⁷ A literature review demonstrated that using chlorhexidine as an adjunct to mechanical plaque removal suppresses the colonisation of dental plaque by potential pathogens.⁸

Factors associated with the development of VAP are oropharyngeal colonisation, gastric colonisation, aspiration and compromised oral health.⁹
lung defences. Micro-aspiration of bacteria-laden secretions that pool above the endotracheal cuff of intubated patients leads to colonisation of the respiratory tract.

Chlorhexidine is a cationic chlorphenyl bis-biguanide antiseptic agent. It has been used as an oral disinfectant in mechanically ventilated patients because of its ability to bind to oral tissues with subsequent slow release of antiseptic properties and therefore a long period of antibacterial action.

Significance of this research
Studies focusing on oral care in critically ill adult patients, specifically with the concurrent use of chlorhexidine, have not provided sufficient evidence of VAP prevention. The primary aim of this study was to systematically appraise and review evidence on the effectiveness of chlorhexidine as a broad-spectrum oral disinfectant to reduce the incidence of VAP in mechanically ventilated adult patients versus a control or placebo. The efficacy of chlorhexidine was determined in the combined studies when used with other comparators including Listerine, normal saline rinse, bicarbonate isotonic rinse, serum rinse, placebos and power tooth brushing. The secondary aim was to systematically summarise evidence on the use of chlorhexidine in reducing mortality.

Criteria for selection of studies

Types of studies. Randomised controlled trials (RCTs) published in English – studies using comparative groups to investigate oral chlorhexidine as a decontaminant in the prevention of VAP in adult mechanically ventilated, critically ill patients versus a control or placebo were considered.

Types of interventions. We focused on studies that reported on the use of oral chlorhexidine versus tooth brushing, placebo or other comparators as oral care interventions to reduce VAP in adult mechanically ventilated, critically ill patients.

Types of participants. Participants in the studies had to be mechanically ventilated, admitted to an ICU, critically ill and aged 18 years or older. A positive culture after intubation is indicative of VAP and diagnosed as such.

Types of outcome measures. The primary outcome of interest was a reduction in the incidence of VAP in mechanically ventilated adult ICU patients with use of chlorhexidine. The secondary outcome was a reduction in mortality. We defined VAP as pneumonia occurring in a patient 48 hours or more after intubation with an endotracheal tube or tracheostomy tube, and which was not present before.

Exclusion criteria. Studies not investigating VAP, even when chlorhexidine was used, were excluded. Studies of patients under the age of 18 years, a clinical diagnosis of pneumonia at the start of the study, extubated patients, edentulous patients and patients with a known allergy and hypersensitivity to chlorhexidine were excluded. Exclusion criteria for this systematic review were a high attrition rate of greater than 20% and unavailability of the full text article.

Methodology

Search methods for identification of studies

Electronic searches. An extensive literature search of published clinical trials reporting on VAP prevention with the use of chlorhexidine in oral care was undertaken. Peer-reviewed publications were searched between June 2010 and July 2011. Sources for relevant studies included the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index of Nursing and Allied Health (CINAHL) and MEDLINE from inception to present. Literature searches were done using Medical Subject Headings (MeSH). The following MeSH terms were used for the search: ventilator-associated pneumonia, VAP, chlorhexidine, hospital-acquired pneumonia, nosocomial infections, mechanically ventilated patients, intensive care, mouthwash, mouth care, oral care, oral hygiene and dental care. The search strategy for MEDLINE was as follows: randomised controlled trial[pt] OR controlled clinical trial[pt] AND (ventilator-associated pneumonia OR VAP OR hospital acquired pneumonia OR nosocomial infections) AND (chlorhexidine OR mouthwash OR mouth care OR oral care OR oral hygiene OR dental care). In total 86 articles were retrieved electronically, of which eight were trials chosen for inclusion in this systematic review.
Searching for other resources. Reference lists of all relevant articles and textbooks were searched for further relevant studies. Experts in critical care nursing, critical care medicine, infection control, microbiology and dentistry were consulted to identify other studies. Hand searching (pearling) of reference lists of all potentially eligible papers (N=8) was performed and summaries from conference proceedings were examined.

Data collection and analysis

Selection of studies. The abovementioned search strategies were independently employed by the reviewers after initially considering the titles of the articles relevant to the study, by searching with the use of the following keywords: ventilator-associated pneumonia, chlorhexidine, oral care, mouth care, nosocomial pneumonia. Article abstracts of relevant titles were then retrieved and reviewed with consideration of the inclusion criteria as described in the previous section. Full texts of relevant articles meeting the inclusion criteria were obtained, reviewed and analysed for methodological quality. The reviews were conducted independently by two reviewers, with a third reviewer available for consultation in the case of disagreements not being resolved by discussion.

Data extraction and management

Selection of studies. A data extraction tool was developed and utilised by the two reviewers to extract and collect information from the studies relevant for this review. A pilot study was conducted to determine the feasibility of the study, test search range, assessment and extraction tools.

Assessment of risk of bias in included studies. Methodological quality was assessed by two reviewers using the Cochrane quality assessment form, which addressed both external and internal validity.

Measures of treatment effect. The effect measure of choice was the risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous data and weighted mean difference using the random effects model (Mantel-Haenszel method). The p-value was set at 0.05.

Unit of analysis. All included studies randomised participants to a treatment group or a control group.

Table I. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Chlorhexidine dosing schedule</th>
<th>Loss to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeRiso et al.</td>
<td>Cardiothoracic (open-heart surgery)</td>
<td>Chlorhexidine gluconate 0.12%</td>
<td>Placebo</td>
<td>0.5 oz/15 ml chlorhexidine 0.12% solution used as rinse pre-operatively; twice daily postoperatively until discharge</td>
<td>None</td>
</tr>
<tr>
<td>Fourrier et al.</td>
<td>Medical-surgical ICU</td>
<td>Chlorhexidine 0.2%</td>
<td>Standard oral care with bicarbonate isotonic serum rinse</td>
<td>After mouth rinsing and oropharyngeal aspiration, gel 3 times a day during ICU stay</td>
<td>None</td>
</tr>
<tr>
<td>Fourrier et al.</td>
<td>Medical-surgical ICU</td>
<td>Chlorhexidine gluconate 0.2%</td>
<td>Placebo</td>
<td>Oral gel applied 3 times daily during ICU stay for 28 days</td>
<td>One (0.87%) secondarily excluded (early antibiotics therapy)</td>
</tr>
<tr>
<td>Houston et al.</td>
<td>Cardiothoracic (open-heart surgery)</td>
<td>Chlorhexidine gluconate 0.12%</td>
<td>Listerine</td>
<td>15 ml oral rinse postoperatively and twice daily for 10 days until death, extubation, tracheostomy or diagnosis of pneumonia</td>
<td>7.7% due to death and tracheostomy</td>
</tr>
<tr>
<td>Koeman et al.</td>
<td>Mixed ICUs</td>
<td>Chlorhexidine 2%</td>
<td>Placebo</td>
<td>Approximately 2 cm paste to buccal cavity, until VAP diagnosed, death or extubation</td>
<td>1.55% due to consent: 1 in placebo group and 2 in chlorhexidine group</td>
</tr>
<tr>
<td>Pobo et al.</td>
<td>Medical-surgical ICU</td>
<td>Chlorhexidine digluconate 0.12%</td>
<td>Power tooth brushing</td>
<td>Gauze containing 20 ml chlorhexidine digluconate 0.12% to all oral surfaces or 10 ml chlorhexidine injected into oral cavity, 8-hrly, for 28 days; power tooth brushing 8-hrly</td>
<td>2.7% early introduction (&lt;48 h) of antibiotic since randomisation</td>
</tr>
<tr>
<td>Scannapieco et al.</td>
<td>Trauma ICU</td>
<td>Chlorhexidine gluconate 0.12%</td>
<td>Placebo</td>
<td>Chlorhexidine 0.12% solution or control twice daily as oral topical treatment, for up to 21 days, until ICU discharge or death</td>
<td>16.57% secondary to death, tracheostomy</td>
</tr>
<tr>
<td>Tantipong et al.</td>
<td>ICU and general medical ward</td>
<td>Chlorhexidine 2%</td>
<td>Normal saline</td>
<td>15 ml chlorhexidine solution or normal saline 4 times per day until extubation</td>
<td>None</td>
</tr>
</tbody>
</table>
Dealing with missing data. Attempts to contact authors concerned were made when pertinent data were missing from the included trials. Missing data were regarded as the absence of any results adding weight to the study and insufficient reporting on study outcomes.

Assessment of heterogeneity. Pooled effect sizes of RRs were estimated using the random effects (Mantel-Haenszel) model, and 95% CIs were presented. Heterogeneity was calculated using $I^2 = \left[ \frac{Q - df}{Q} \right] \times 100\%$, where $Q$ is the chi-squared statistic and $df$ is its degrees of freedom. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. An $I^2$ value of less than 40% was considered not important, 40 - 60% was considered moderate heterogeneity, and 60 - 75% was regarded as substantial heterogeneity. Values of 75% and above were regarded as indicating considerable heterogeneity.

Assessment of reporting biases. Reporting bias was not identified in any of the included studies.

Data synthesis. All relevant data were entered into a statistical analysis software package known as Review Manager (version 5.1, Cochrane Collaboration) for analysis. The effect measure of choice was RR with 95% CIs for dichotomous data and weighted mean difference with 95% CIs for continuous data using the random effects (Mantel-Haenszel) model. Forest plots were used to demonstrate the effect of interventions.

Subgroup analysis and investigation of heterogeneity. Subgroup analyses were completed on trials after identifying clinical diversity in respect of the differing concentrations of chlorhexidine used within these included trials and comparisons.

Reliability and validity. Reliability, validity and quality assessment of study data were ensured by piloting and using a standardised data extraction form.

Results

Results of search. Results of the search are shown in Fig. 1. Of the 86 titles and abstracts identified, 94.2% (81) were from electronic searches and the remaining 5.8% (5) were identified from manual reference checks. The reviewers excluded 71 articles because the titles were not relevant to the review. After reading the abstracts of the remaining 15 studies, 4 studies were excluded for failing to report outcomes as VAP. Full articles were retrieved for the 11 studies and appraised for methodological quality. Three articles were excluded following this process. Meta-analysis was performed on 8 studies. A total of 1 930 participants were included in the analysis.

Description of selected studies. Studies included in this review (N=8) were all RCTs. The trials collectively enrolled a total of 1 930 patients, of whom 947 received chlorhexidine (treatment group) as varying oral formulations.

Studies included. The eight studies included in this review were DeRiso et al.,¹¹ Fourrier et al.,¹² Fourrier et al.,¹⁰ Houston et al.,¹³ Koeman et al.,¹⁴ Pobo et al.,¹⁵ Scannapieco et al. and Tantipong et al.¹⁶

Studies excluded. Three studies were excluded after critical appraisal of methodologies. One trial was excluded after repeated unsuccessful attempts to contact the authors for information.¹⁷ The second study¹⁸ could not be located, and the third¹⁹ was excluded after the full text review revealed an attrition rate of 50%.

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of VAP</th>
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<tbody>
<tr>
<td>DeRiso et al.¹¹</td>
<td>New or progressive pulmonary infiltrate, fever, leucocytosis, purulent tracheal secretions</td>
</tr>
<tr>
<td>Fourrier et al.¹²</td>
<td>Temperature &gt;38°C or &lt;36°C; presence of infiltrate on chest radiograph; leucocytosis or leucopenia; positive quantitative culture of tracheal aspirate (10⁶ colony-forming units (CFUs)/ml) and/or positive culture of BAL (10⁶ CFUs/ml)</td>
</tr>
<tr>
<td>Fourrier et al.⁶</td>
<td>Temperature &gt;38°C or &lt;36°C; presence of infiltrate on chest radiograph; leucocytosis or leucopenia; positive quantitative culture of tracheal aspirate (10⁶ CFUs/ml) and/or positive culture of BAL (10⁶ CFUs/ml)</td>
</tr>
<tr>
<td>Houston et al.¹³</td>
<td>New or progressive infiltrate; The Centre for Disease and infection Control postulates the following criteria for diagnosing nosocomial pneumonia: fever and pulmonary infiltrate; nature of tracheo-bronchial secretions; degree of leucocytosis; microbial culture results; semi-quantitative sputum samples at extubation</td>
</tr>
<tr>
<td>Koeman et al.¹⁴</td>
<td>Chest radiograph with new, persistent or progressive infiltrate in combination with at least 3 of the following criteria: temperature &gt;38°C or &lt;35.5°C; blood leucocytosis or leucopenia; purulent tracheal aspirate; positive semi-quantitative culture from tracheal aspirates (cut-off ≥10⁵ CFUs/ml); daily Clinical Pulmonary Infection Scores (CPIS) done</td>
</tr>
<tr>
<td>Pobo et al.¹⁵</td>
<td>Presence of new or progressive pulmonary opacities on chest radiograph, purulent respiratory secretions, fever (&gt;38°C), leucocytosis &gt;10 000 cells/ml, quantitative respiratory samples with at least one pathogenic organism (protected specimen brush yielding ≥10⁵ or tracheal aspirates ≥10⁵ CFUs/ml)</td>
</tr>
<tr>
<td>Scannapieco et al.⁵</td>
<td>CPIS scores based on following elements: partial pressure of arterial oxygen (PaO₂)/fraction of inspired oxygen (FiO₂); infiltrate on chest radiograph, fever, leucocytosis and purulent secretions; CPIS scores or 6 or more triggered BAL sampling of lower airways</td>
</tr>
<tr>
<td>Tantipong et al.¹⁶</td>
<td>Chest radiograph with new, persistent or progressive infiltrate in combination with at least 3 of the following criteria: temperature &gt;38°C or &lt;35.5°C, leucocytosis or leucopenia, purulent tracheal aspirate, tracheal aspirate and/or semi-quantitative sample of tracheal aspirate positive for pathogenic bacteria</td>
</tr>
<tr>
<td>Study</td>
<td>Adequate sequence generation</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>DeRiso et al.11</td>
<td>Low risk Computer-driven random number generated</td>
</tr>
<tr>
<td>Fourrier et al.12</td>
<td>Low risk Computer-generated balanced randomisation table</td>
</tr>
<tr>
<td>Fourrier et al.5</td>
<td>Low risk Block randomisation stratified by site</td>
</tr>
<tr>
<td>Houston et al.13</td>
<td>Low risk Consecutively randomised by medical record numbers</td>
</tr>
<tr>
<td>Koeman et al.14</td>
<td>Low risk Randomly assigned by computerised randomisation stratified by hospital/centre</td>
</tr>
<tr>
<td>Pobo et al.15</td>
<td>Low risk Randomisation by computer-generated list</td>
</tr>
<tr>
<td>Scannapieco et al.7</td>
<td>Low risk Randomised by web-based subject enrolment system with protocol specification files</td>
</tr>
<tr>
<td>Tantipong et al.16</td>
<td>Low risk Stratified randomisation according to gender and hospital location</td>
</tr>
</tbody>
</table>

*Unclear = lack of information or unknown risk of bias.
Studies included in review

Characteristics of included studies (Table I)

Trial settings. Trials were conducted in the ICU setting where patients are mechanically ventilated and dependent on nursing care to meet their oral care needs (Table I). These settings included cardiothoracic ICUs (N=2), trauma ICUs (N=1), medical ICUs (N=1) and mixed medical-surgical ICUs (N=4). Some studies were single-centre focused (N=5) while others were multi-centre (N=3).

Intervention groups. The oral chlorhexidine preparations varied among the experimental groups. The majority of the included trials used chlorhexidine in the form of an oral solution. The trial by Pobo et al. used chlorhexidine digluconate, which differs from chlorhexidine gluconate only on a molecular binding level. This difference is insignificant and does not affect the potency or effect of chlorhexidine, so this study was regarded as included in the subgroup analysis done on the varying concentration levels of chlorhexidine in the treatment groups. The majority of trials used chlorhexidine 0.12% (N=4), while others used chlorhexidine 0.2% (N=2) and 2% concentrations (N=2).

Comparison groups. Most of the comparison groups received placebos in the form of oral solutions, gels or pastes with a similar taste, smell and consistency to the chlorhexidine (N=5). The comparison groups also received power tooth brushing (N=1), normal saline oral rinse (N=1) or phenolic rinse (Listerine) (N=1).

Loss to follow-up. Loss to follow-up was low in the included trials, ranging from 0% to 16.5%.

Diagnostic criteria. Diagnostic measures used to diagnose VAP included semi-quantitative microbiology techniques and quantitative microbiology techniques (Table II).

Risk of bias in included studies (Table III)

Methodological assessment. Computerised randomisation was the most frequently used method in the trials (N=5). Other means of randomisation included block randomisation stratified by site (N=1), stratified randomisation according to gender and hospital location (N=1), and consecutive randomisation by medical record numbers (N=1). Allocation
concealment was achieved in most of the trials by having pharmacy staff complete the randomisation schedule. Other methods of allocation concealment included opaque sealed envelopes and web-based subject identity numbers.

Results of pooling trials
Outcomes of completed trials are shown in Table IV. The use of chlorhexidine was supported in the eight trials, with an RR of 0.64 (95% CI 0.44 - 0.91; p=0.18). The pooled results showed evidence of the effectiveness of chlorhexidine in reducing VAP, the test for overall effect being reflected as Z=2.47 (p=0.01). Fig. 2 shows a good overlap of CIs, although most individual studies did not show benefit in the use of chlorhexidine in reducing VAP.

Mortality
Results of all eight trials were available for pooling and analysis of mortality (Fig. 3). DeRiso et al.11 reported findings of a reduction in mortality in their chlorhexidine 0.12% treatment group, the reduction being 1.16% as opposed to 5.56% in the comparison groups. These findings are also reflected within the pooled analysis (Fig. 3). Mortality, a secondary outcome of interest in this review, appeared overall to be unaffected by chlorhexidine with an RR of 1.12 (95% CI 0.86 - 1.46; p=0.18).

Cost-effectiveness of chlorhexidine
Tantipong et al.14 reported that use of chlorhexidine 2% was cost-effective, the mean cost per patient being calculated as 10 times less than the cost of antibiotics needed to treat an episode of VAP. Koeman et al.15 also found chlorhexidine to be a cost-effective and safe intervention in VAP prevention, and known side-effects were absent in their trial.

Side-effects associated with chlorhexidine use
Side-effects related to 2% chlorhexidine oral solution use were observed and reported in 9.8% of participants in the trial by Tantipong et al.14 These side-effects, reported to be mild, reversible and affecting mainly the oral mucosa, were observed in 10 of the 102 patients randomised to the chlorhexidine treatment group. After personnel were instructed to clean the oropharyngeal mucosa more gently, the incidence of irritation was reduced.⁶ Koeman et al.16 reported that 1 patient in the chlorhexidine-Colistin group (arm excluded from this study) developed tongue oedema. None of the other studies reported side-effects related to chlorhexidine use.

Table IV. Outcomes of completed trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial study outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Riso et al.11</td>
<td>Overall nosocomial infection rates, other infections, non-prophylactic IV antibiotic use, length of stay in hospital, duration of intubation, need for reintubation and in-hospital mortality</td>
</tr>
<tr>
<td>Fourrier et al.12</td>
<td>Primary outcome was the incidence of nosocomial bacteraemia, bronchitis and VAP in ICU. Secondary outcomes were incidence of VAP and bronchitis, incidence of VAP, mortality and length of stay in ICU and total omega score and omega-day score</td>
</tr>
<tr>
<td>Fourrier et al.6</td>
<td>Primary outcome was the incidence of nosocomial bacteraemia, bronchitis and VAP in ICU. Secondary outcomes were incidence of VAP and bronchitis, incidence of VAP, mortality and length of stay in ICU and total omega score and omega-day score</td>
</tr>
<tr>
<td>Houston et al.13</td>
<td>Reduction of bacterial colonisation of the respiratory tract and nosocomial pneumonia and incidence of nosocomial pneumonia</td>
</tr>
<tr>
<td>Koeman et al.14</td>
<td>Primary outcome measure was time to VAP. Secondary endpoints included oral colonisation with Gram-positive or Gram-negative micro-organisms, endotracheal colonisation and all-cause ICU mortality</td>
</tr>
<tr>
<td>Pobo et al.15</td>
<td>Incidence of VAP. Secondary endpoints were days of mechanical ventilation, length of stay, antibiotic-free days and ICU mortality</td>
</tr>
<tr>
<td>Scannapieco et al.9</td>
<td>Primary outcomes were dental plaque score and colonisation of the oral cavity by respiratory pathogens. Secondary outcomes were diagnosis of pneumonia in mechanically ventilated patients, mortality, length of ventilation in ICU and length of stay in ICU</td>
</tr>
<tr>
<td>Tantipong et al.14</td>
<td>Development of VAP and oropharyngeal colonisation with Gram-negative bacilli</td>
</tr>
</tbody>
</table>

Random effects analysis – sensitivity analysis performed with exclusion of trials conducted in cardiothoracic ICUs.
Discussion

Eight RCTs met the inclusion criteria. Using the random effects (Mantel-Haenszel) model, the pooled RR was 0.64 (95% CI 0.44 - 0.91; p = 0.18). The probability of mechanically ventilated patients acquiring VAP with the use of chlorhexidine is 36% less likely than in controls, and heterogeneity was low (I²=31%). These findings were consistent with a previous study (Chlebicki and Safdar20) that found a pooled RR of 0.70 (95% CI 0.48 - 1.04; p = 0.08).

Subgroup analysis was performed on the varying concentrations of chlorhexidine. Chlorhexidine 0.12% and chlorhexidine 0.2%, but failed to show any significant effect. Chlorhexidine 2%, however, demonstrated a more significant effect on the incidence of VAP, with an RR of 0.53 (95% CI 0.31 - 0.91; p = 0.63). A previous meta-analysis produced a similar result to this review with an RR of 0.53 (95% CI 0.31 - 0.91; p = 0.62) for chlorhexidine 2%.21 Chlorhexidine 2% may provide a better reduction of VAP in high-risk patients (those in mixed and medical ICUs). Ironically, chlorhexidine 0.12% and chlorhexidine 0.2% were used in the majority of trials and showed no effect in reducing VAP (Fig. 4). These results support the use of 2% chlorhexidine versus 0.12% chlorhexidine or 0.2% chlorhexidine for reducing VAP in high-risk patients. All studies but one reported that assessors were blinded. Bias could have been introduced to the study that never reported on blinding if the assessors were not blinded.

The trials conducted in cardiothoracic ICUs showed a low incidence of VAP (7 of 443 in the chlorhexidine groups and 18 of 471 in the comparison groups). These observations and findings were consistent with two meta-analyses.20,21 It could be argued further that because the trials by DeRiso et al.11 and Houston et al.19 were performed in cardiothoracic ICUs, they achieved better effect from the use of chlorhexidine. Houston et al.19 reported on participants undergoing aortocoronary bypass graft or valve surgery. DeRiso et al.11 selected patients undergoing coronary artery bypass surgery (CABG), valve and septal surgery, cardiac tumour excision and combined CABG and valve surgery. It can be assumed that because these patients were having elective cardiac surgery they would generally have a better physiological status secondary to cardiac surgery work-up and therefore better co-morbid conditions, with the duration of ventilation rarely exceeding 24 - 48 hours. Benefit to the participants would therefore be more impressive and significant. Sensitivity analysis was attempted using the random effects model, and extracting data from only these two trials revealing an RR of 0.28 (95% CI 0.12 - 0.64). In mixed medical populations, the period of ventilation and intubation usually exceeds 24 - 48 hours, length of stay and ventilation is prolonged, and patients generally have more underlying co-morbidities, making them more prone to developing VAP.

Mortality was unaffected by the use of chlorhexidine, with an RR of 1.12 (95% CI 0.69 - 1.45; p = 0.18 and I² = 31%) indicating moderate clinical heterogeneity. Findings were again consistent with those of Chlebicki and Safdar,21 Chan et al.17 and Labeau et al.20 linking heterogeneity to the effect of chlorhexidine on mortality. Only one study reported a reduction in mortality in relation to the use of oral chlorhexidine. Mixed ICU patients and medical patients generally tend to have more co-morbidities, resulting in higher mortality rates. The trial by DeRiso et al.11 found a reduction in mortality. These findings may have resulted from underlying heterogeneity associated with trial settings and clinical diversity among the patient populations. This study took place in the cardiothoracic unit and the patients had undergone open-heart surgery.

Aformal cost analysis of chlorhexidine has not yet been undertaken, but individual trials have reported it to be a cost-effective, safe alternative in comparison with the cost of treating an episode of VAP, or use of prophylactic antibiotic therapy. Side-effects in the individual trials included in this meta-analysis were minimal, so chlorhexidine may prove to be a safe alternative to prophylactic antibiotics.

Conclusion

Eight studies published in English were included in this systematic review and contributed to its overall completeness. Chlorhexidine proved to be beneficial in the prevention of VAP, with 2% chlorhexidine appearing most effective. No evidence of a reduction in mortality with the use of chlorhexidine was found. It is recommended that further rigorous studies be conducted on the optimal concentration, administration procedures, dosage and cost-effectiveness of chlorhexidine. Although the use of 2% chlorhexidine may be most effective in reducing the incidence of VAP, owing to the few trials it was tested in, further research is recommended. Finally, more evidence is needed from developing countries.

References


