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 I^2.

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 chlorexidine group (RR 0.64, 95% CI 0.44 - 0.91). The variation between the included studies was very small (χ^2=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 gingivo-dental 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.[6] A literature review demonstrated that using chlorhexidine as an adjunct to mechanical plaque removal suppresses the colonisation of dental plaque by potential pathogens.[7]

Factors associated with the development of VAP are oropharyngeal colonisation, gastric colonisation, aspiration and compromised

lung defences.[8] Micro-aspiration of bacteria-laden secretions that pool above the endotracheal cuff of intubated patients leads to colonisation of the respiratory tract.[2]

Chlorhexidine is a cationic chlorophenyl 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.[9]

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.[10]

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.

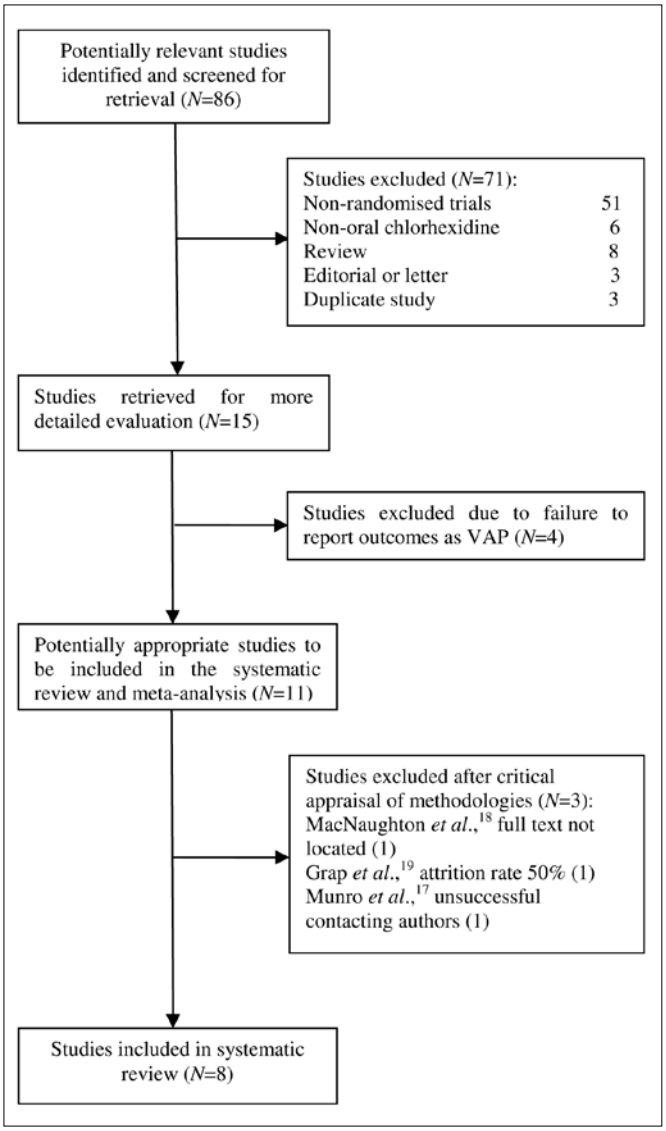

Fig. 1. Flow diagram of included studies.

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 two 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

Study	Population	Intervention	Comparison	Chlorhexidine dosing schedule	Loss to follow-up
DeRiso *et al.*[11]	Cardiothoracic (open-heart surgery)	Chlorhexidine gluconate 0.12%	Placebo	0.5 oz/15 ml chlorhexidine 0.12% solution used as rinse pre-operatively; twice daily postoperatively until discharge	None
Fourrier *et al.*[12]	Medical-surgical ICU	Chlorhexidine 0.2%	Standard oral care with bicarbonate isotonic serum rinse	After mouth rinsing and oropharyngeal aspiration, gel 3 times a day during ICU stay	None
Fourrier *et al.*[6]	Medical-surgical ICU	Chlorhexidine gluconate 0.2%	Placebo	Oral gel applied 3 times daily during ICU stay for 28 days	One (0.87%) secondarily excluded (early antibiotics therapy)
Houston *et al.*[13]	Cardiothoracic (open-heart surgery)	Chlorhexidine gluconate 0.12%	Listerine	15 ml oral rinse postoperatively and twice daily for 10 days until death, extubation, tracheostomy or diagnosis of pneumonia	7.7% due to death and tracheostomy
Koeman *et al.*[14]	Mixed ICUs	Chlorhexidine 2%	Placebo	Approximately 2 cm paste to buccal cavity, until VAP diagnosed, death or extubation	1.55% due to consent: 1 in placebo group and 2 in chlorhexidine group
Pobo *et al.*[15]	Medical-surgical ICU	Chlorhexidine digluconate 0.12%	Power tooth brushing	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	2.7% early introduction (<48 h) of antibiotic since randomisation
Scannapieco *et al.*[9]	Trauma ICU	Chlorhexidine gluconate 0.12%	Placebo	Chlorhexidine 0.12% solution or control twice daily as oral topical treatment, for up to 21 days, until ICU discharge or death	16.57% secondary to death, tracheostomy
Tantipong *et al.*[16]	ICU and general medical ward	Chlorhexidine 2% oral	Normal saline	15 ml chlorhexidine solution or normal saline 4 times per day until extubation	None

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=[Q-df/Q]×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.*,[6] Houston *et al.*,[13] Koeman *et al.*,[14] Pobo *et al.*,[15] Scannapieco *et al.*[9] 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 study[18] could not be located, and the third[19] was excluded after the full text review revealed an attrition rate of 50%.

Table II. VAP definitions/diagnostic criteria

Study	Definition of VAP
DeRiso *et al.*[11]	New or progressive pulmonary infiltrate, fever, leucocytosis, purulent tracheal secretions
Fourrier *et al.*[12]	Temperature >38˚C or <36˚C; presence of infiltrate on chest radiograph; leucocytosis or leucopenia; positive quantitative culture of tracheal aspirate (10^6 colony-forming units (CFUs)/ml) and/or positive culture of BAL (10^6 CFUs/ml)
Fourrier *et al.*[6]	Temperature >38˚C or <36˚C; presence of infiltrate on chest radiograph; leucocytosis or leucopenia; positive quantitative culture of tracheal aspirate (10^6 CFUs/ml) and/or positive culture of BAL (10^6 CFUs/ml)
Houston *et al.*[13]	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
Koeman *et al.*[14]	Chest radiograph with new, persistent or progressive infiltrate in combination with at least 3 of the following criteria: temperature >38˚C or <35.5˚C; blood leucocytosis or leucopenia; purulent tracheal aspirate; positive semi-quantitative culture from tracheal aspirates (cut-off ≥10^5 CFUs/ml); daily Clinical Pulmonary Infection Scores (CPIS) done
Pobo *et al.*[15]	Presence of new or progressive pulmonary opacities on chest radiograph, purulent respiratory secretions, fever (>38˚C), leucocytosis >10 000 cells/ml, quantitative respiratory samples with at least one pathogenic organism (protected specimen brush yielding ≥10^3 or tracheal aspirates ≥10^5 CFUs/ml)
Scannapieco *et al.*[9]	CPIS scores based on following elements: partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), infiltrate on chest radiograph, fever, leucocytosis and purulent secretions; CPIS scores or 6 or more triggered BAL sampling of lower airways
Tantipong *et al.*[16]	Chest radiograph with new, persistent or progressive infiltrate in combination with at least 3 of the following criteria: temperature >38˚C or <35.5˚C, leucocytosis or leucopenia, purulent tracheal aspirate, tracheal aspirate and/or semi-quantitative sample of tracheal aspirate positive for pathogenic bacteria

Table III. Methodological quality/risk of bias assessment

Study	Adequate sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other biases/ potential threats
DeRiso *et al.*[11]	**Low risk** Computer-driven random number generated	**Low risk** Randomisation by the pharmacy	**Low risk** Placebo prepared and dispensed by pharmacy – placebo and treatment identical	**Low risk** All participants randomised were analysed.	**Low risk** All relevant outcomes fully reported on	**Low risk** Nil noted
Fourrier *et al.*[12]	**Low risk** Computer-generated balanced randomisation table	**Low risk** Blinded physicians in charge from results, dental bacteriologists from treatment allocation code	**Low risk** Hygiene nurse and physicians blinded to treatment given	**Low risk** Intention to treat **(ITT)** analysis reported	**Low risk** All relevant outcomes fully reported on	**Low risk** Nil noted
Fourrier *et al.*[6]	**Low risk** Block randomisation stratified by site	**Low risk** Randomisation lists held in sealed envelopes in pharmacy	**Low risk** Investigators blinded to patient assignments	**Low risk** ITT analysis used – one secondary exclusion	**Low risk** All relevant outcomes fully reported	**Low risk** Nil noted
Houston *et al.*[13]	**Low risk** Consecutively randomised by medical record numbers	**Unclear**	**Low risk** Outcome assessor independent person	**Low risk** All outcomes fully reported	**Low risk** All relevant outcomes fully reported	**Low risk**
Koeman *et al.*[14]	**Low risk** Randomly assigned by computerised randomisation stratified by hospital/centre	**Low risk** Experimental and placebo pastes produced and labelled by clinical pharmacy	**Low risk** Intensivists blinded to trail randomisation	**Low risk** ITT employed; exclusions were low	**Low risk** All relevant outcomes fully reported on	**Low risk** Nil noted
Pobo *et al.*[15]	**Low risk** Randomisation by computer-generated list	**Low risk** Randomised by means of opaque sealed envelopes	**Low risk** Investigators and attending physicians blind to group assignment	**Low risk** All participants randomised were analysed	**Low risk** All relevant outcomes fully reported	**High risk** Trial prematurely stopped by steering committee
Scannapieco *et al.*[9]	**Low risk** Randomised by web-based subject enrolment system with protocol specification files	**Low risk** Web-based (computer generated) randomisation preparing individual treatment assignments by subject ID number (SID)	**Low risk** Assignment of treatments blinded to outcome assessors, statisticians and care providers	**Low risk** **ITT** analysis employed	**Low risk** All relevant outcomes fully reported	**Low risk** Nil noted
Tantipong *et al.*[16]	**Low risk** Stratified randomisation according to gender and hospital location	**Low risk** Executed by pharmacy	**Low risk** Blinding of data collectors and outcome assessors	**Low risk** All outcomes reported on	**Low risk** All relevant outcomes fully reported	**Low risk** Nil noted

*Unclear = lack of information or unknown risk of bias.

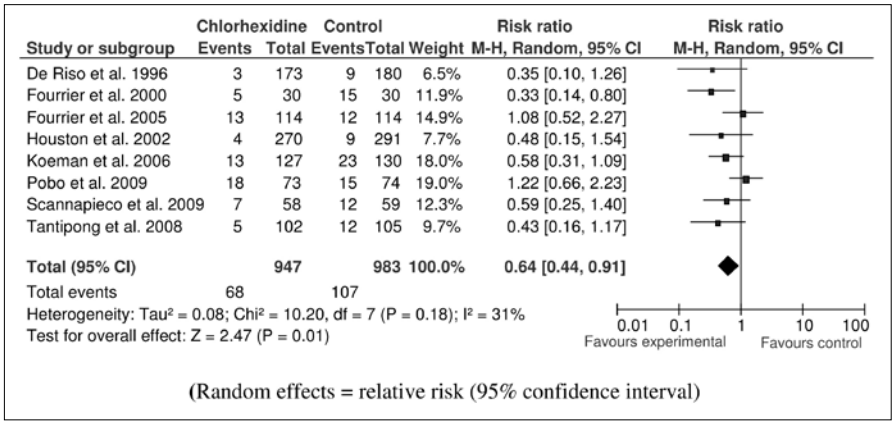

Fig. 2. Random effects analysis: risk of ventilator-associated pneumonia (VAP).

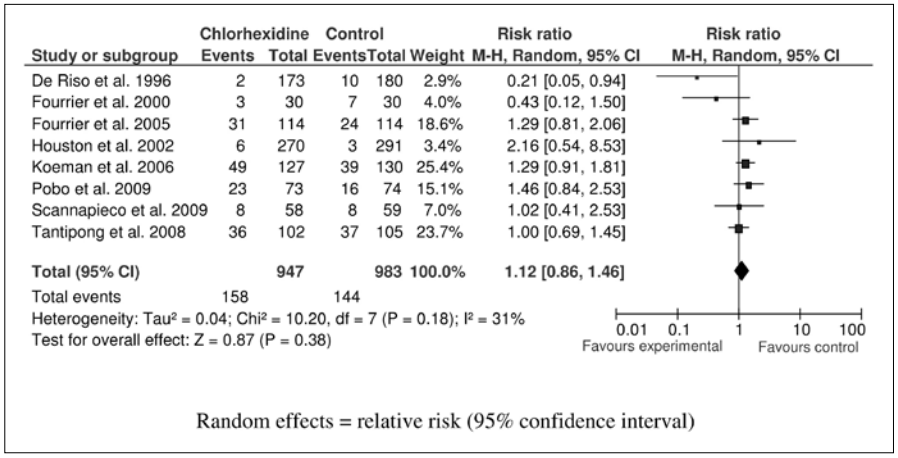

Fig. 3. Random effects analysis – overall effect of chlorhexidine on mortality.

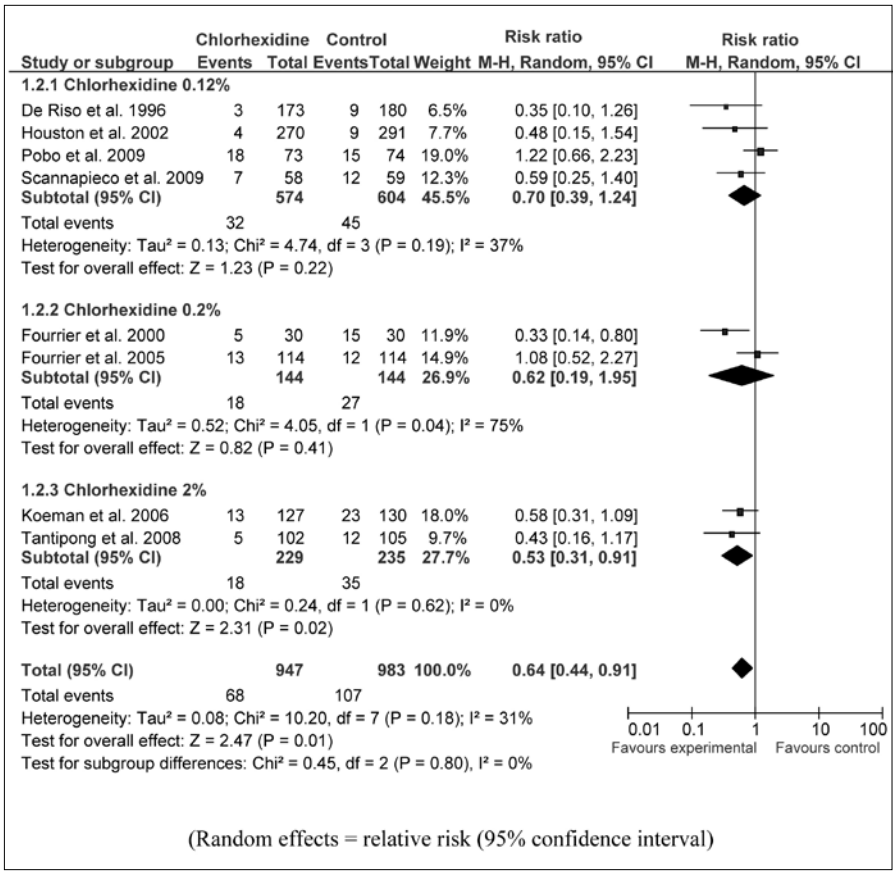

Fig. 4. Subgroup analysis of ventilator-associated pneumonia (VAP) per chlorhexidine level of therapeutic concentration.

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.*[15] 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*.[16] 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*.[14] also found chlorhexidine to be a cost-effective and safe intervention in VAP prevention, and known side-effects were absent in their trial.

Table IV. Outcomes of completed trials

Study	Trial study outcomes
De Riso *et al*.[11]	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
Fourrier *et al*.[12]	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
Fourrier *et al*.[6]	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
Houston *et al*.[13]	Reduction of bacterial colonisation of the respiratory tract and nosocomial pneumonia and incidence of nosocomial pneumonia
Koeman *et al*.[14]	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
Pobo *et al*.[15]	Incidence of VAP. Secondary endpoints were days of mechanical ventilation, length of stay, antibiotic-free days and ICU mortality
Scannapieco *et al*.[9]	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
Tantipong *et al*.[16]	Development of VAP and oropharyngeal colonisation with Gram-negative bacilli

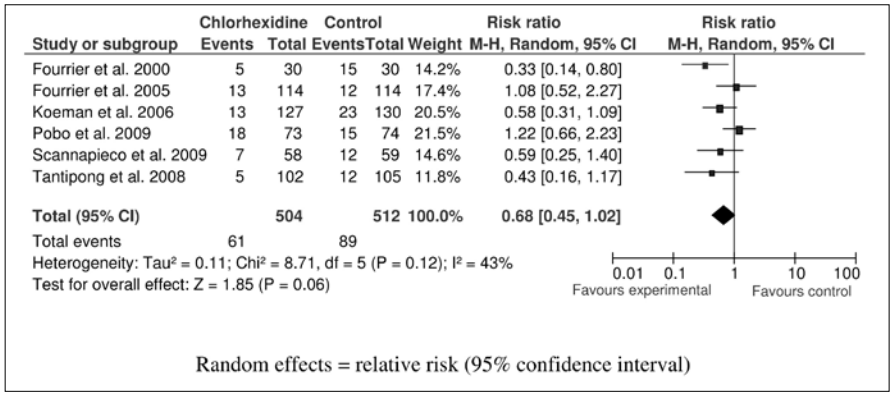

Fig. 5. Random effects analysis – sensitivity analysis performed with exclusion of trials conducted in cardiothoracic ICUs.

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*.[16] 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.[16] Koeman *et al*.[14] 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.

Subgroup and sensitivity analysis. Subgroup analyses were performed on the three common strengths of chlorhexidine to determine their effect on the results (Fig. 4). In the chlorhexidine 0.12% group, 32 of 574 patients developed VAP associated with an RR of 0.70. In the chlorhexidine 0.2% trials, 18 or 144 patients had developed VAP associated with an RR of 0.62. In the chlorhexidine 2% trials, 18 of the 229 patients in the chlorhexidine treatment group were found to develop VAP; the RR was 0.53 (95% CI 0.31 - 0.91; p=0.11). Chlorhexidine 2% therefore demonstrated a better treatment effect. Excluding the Houston and Pobo studies that had methodological concerns, the odds ratio was 0.55 (95% CI 0.36 - 0.86; p=0.33). RR was calculated excluding studies done in cardiothoracic ICUs (Fig. 5). We found a better effect of chlorexidine in these participants (RR 0.28, 95% CI 0.12 - 0.64).

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 (I^2=31%). These findings were consistent with a previous study (Chlebicki and Safdar[21]) 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%.[20] 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.*[13] were performed in cardiothoracic ICUs, they achieved better effect from the use of chlorhexidine. Houston *et al.*[13] 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 I^2=31% indicating moderate clinical heterogeneity. Findings were again consistent with those of Chlebicki and Safdar,[21] Chan *et al.*[22] 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 chlorexidine. 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.

A formal 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

1. American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator associated and healthcare associated pneumonia. Am J Resp Crit Care Med 2005;171:388-416.
2. Augustyn B. Ventilator-associated pneumonia: risk factors and prevention. Critical Care Nurse 2007;27(4):32.
3. Powers J. Managing VAP effectively to optimize outcomes and costs. Nursing Management 2006;37 (11):48D-48G.
4. Centers for Disease Control and Prevention, 2009. August 19 – last update. Healthcare-associated infections: State plans [Homepage of Department of Health & Human Services]. http://www.cdc.gov/ncidod/dhqp/hai/HAI_StatePlan081909WebConference.pdf (accessed 20 July 2010).
5. Munro CL, Grap MJ. Oral health and care in the intensive care unit: state of the science. Am J Crit Care 2004;13(1):25-34.
6. Fourrier F, Dubois D, Pronnier P, et al. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: A double-blind placebo-controlled multicenter study. Crit Care Med 2005;33(8):1728-1735.
7. O'Reilly M. Oral care of the critically ill: a review of the literature and guidelines for practice. Aust Crit Care 2003;16(3):101-110.
8. Morton PG, Fontaine DK, Hudak CM, Gallo BM. Critical Care Nursing: A Holistic Approach. Philadelphia: Lippincott Williams & Wilkins, 2005.
9. Scannapieco F, Yu J, Raghavendran K, et al. A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. Crit Care 2009;13(4):R117. doi:10.1186/cc7967
10. Wagh H, Acharya D. Ventilator-associated pneumonia – an overview. British Journal of Medical Practitioners 2009;2(2):16-19.
11. DeRiso AJ, Ladowski JS, Dillon, TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 1996; 109(6):1556-1561.
12. Fourrier F, Cau-Pottier E, Boutigny H, Roussel-Delvallez M, Jourdain M, Chopin C. Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. Intensive Care Med 2000;26:1239-1247.
13. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. Am J Crit Care 2002;11:567-570.
14. Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006;173:1348-1355.
15. Pobo A, Lisboa T, Rodriguez A, et al. A randomized trial of dental brushing for preventing ventilator-associated pneumonia. Chest 2009;136(2):433-439.
16. Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2008;29(2):131-136.
17. Munro CL, Grap MJ, Jones DJ, McClish DK, Sessler CN. Chlorhexidine, toothbrushing, and preventing ventilator-associated pneumonia in critically ill adults. Am J Crit Care 2009;18(5):428-437.
18. MacNaughton PD, Bailey J, Donlin N, Branfield P, Williams A, Rowswell H. A randomised controlled trial assessing the efficacy of oral chlorhexidine in ventilated patients. European Society of Intensive Care Medicine, 17th Annual Congress, Berlin, Germany. Intensive Care Med 2004;30(suppl):S5-S18.
19. Grap MJ, Munro CL, Elswick RK Jr, Sessler CN, Ward KR. Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: a pilot study. Heart Lung 2004;33:83-91.
20. Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. Lancet Infect Dis 2011;39(4):347-358.
21. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. Crit Care Med 2007;35:595-602.
22. Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. BMJ 2007;334:889-899.