Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis
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CRD summary
This review reported that topical application of chlorhexidine is useful for preventing ventilator-associated pneumonia in mechanically ventilated patients. This was a well-conducted review, but the conclusions should have been slightly more cautious given the clinical and statistical differences between the studies and the unknown quality of some of the included trials.

Authors' objectives
To assess the efficacy of topical chlorhexidine for the prevention of ventilator-associated pneumonia (VAP).

Searching
PubMed (including MEDLINE), Current Contents, CINAHL, DARE and the Cochrane Library were searched from inception to April 2006; keywords were provided. The authors also searched Conference Papers Index, BIOSIS RRM and the National Institutes of Health website listings of ongoing trials, and handsearched abstracts from several conference meetings. Reference lists of retrieved articles were checked for additional studies, and experts in the field were contacted for unpublished studies. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared topical oropharyngeal chlorhexidine with placebo or standard care were eligible for inclusion. The included studies evaluated chlorhexidine applied as a rinse, gel, spray or swab at varying dosing schedules. The comparators included placebo, phenolic oral rinse (Listerine), isotonic sodium bicarbonate with sterile oropharyngeal aspiration, or standard oral care.

Participants included in the review
The authors did not specify inclusion criteria for the participants. The studies included cardiothoracic intensive care unit (ICU) patients, medicosurgical ICU patients, or all trauma and surgical patients who required endotracheal intubation and mechanical ventilation.

Outcomes assessed in the review
Studies that reported VAP as an outcome were eligible for inclusion. Other outcomes of interest were mortality, the incidence rate of VAP (reported as cases per 1,000 mechanically ventilated patient-days), length of ICU stay, length of hospital stay, duration of mechanical ventilation, the time from intubation to VAP occurrence and impact on colonisation by oral flora. Various definitions of VAP were used in the included studies.

How were decisions on the relevance of primary studies made?
Two reviewers independently applied the inclusion criteria.

Assessment of study quality
The authors did not explicitly state how they assessed quality. Two reviewers were involved in the data extraction process which reported randomisation methods, blinding and intention-to-treat analysis.

Data extraction
Two reviewers independently extracted the data using a standard form, and any disagreements were resolved through consensus. When necessary, authors were contacted to obtain additional information for statistical analysis. Relative risks (RRs) were calculated for dichotomous outcomes.
Methods of synthesis
How were the studies combined?
A meta-analysis was used to estimate the pooled RR with 95% confidence intervals (CIs) using random-effects (DerSimonian and Laird) and fixed-effect (Mantel-Haenszel) models. One study had multiple (three) trial arms and a combination treatment arm was excluded from the analysis. Publication bias was assessed using a funnel plot and Egger's statistical test.

How were differences between studies investigated?
The Cochran Q statistic and I-squared statistic were used to test for statistical heterogeneity. Subgroup analyses examining cardiac surgery patients and sensitivity analyses including only the largest published RCTs were conducted.

Results of the review
Seven RCTs (n=1,650) were included. The number of patients ranged from 5 to 291.

Six of the 7 included studies reported methods of randomisation, including block randomisation, computer-generated randomisation methods, and consecutive randomisation based on medical record numbers. Blinding was reported in 6 studies. Intention-to-treat analysis was performed in 5 studies.

Overall, 9% of participants developed VAP in the treatment group compared with 12% in the comparison group (7 studies; RR 0.74, 95% CI: 0.56, 0.96, p=0.03). When a random-effects model was used, there was no significant difference between the groups (7 studies; RR 0.70, 95% CI: 0.48, 1.04, p=0.08). No significant heterogeneity was found when using the Cochran Q statistic, but I-squared was 43%. When the analysis was limited to cardiac surgery patients, the results were significant in favour of treatment (2 studies; RR 0.41, 5% CI: 0.17, 0.98, p=0.04). When the analysis was restricted to 5 published RCTs, the results of the random-effects analysis were also significant (RR 0.57, 95% CI: 0.39, 0.83).

Overall, 16% of participants died in the treatment group compared with 14% in the comparison group (6 studies; RR 1.07, 95% CI: 0.76, 1.51, p=0.69).

The funnel plot did not suggest the presence of publication bias.

Cost information
Three studies estimated the costs of chlorhexidine: one reported a cost of $700 per year for cardiac surgery patients; another reported a $40,000 savings due to a reduction in antimicrobial use; and one calculated that 8 days of treatment cost less than $100.

Authors’ conclusions
Topical application of chlorhexidine is useful for preventing VAP in mechanically ventilated patients. The benefit was most evident in cardiac surgery patients.

CRD commentary
The review question was clear and inclusion criteria were well defined for the intervention, study type and outcomes. The search was well conducted and a funnel plot was used to assess any publication bias. The authors assessed some validity criteria, but could have used this information in their sensitivity analyses. Two reviewers were involved in the review process, which reduces the risk of reviewer bias. Details of the included studies were presented, although it appears that some of the data were not well reported in the original studies. The authors reported heterogeneity between the studies and explored reasons for it. This was a very well-conducted review, but the conclusions should have been slightly more cautious given the clinical and statistical differences between the studies and the unknown quality of some of the included trials.

Implications of the review for practice and research
Practice: The authors stated that topical chlorhexidine is beneficial in preventing VAP.
Research: The authors stated that a large RCT is needed to examine the effect of chlorhexidine on mortality. Future trials should also document any adverse events. Studies are needed to address the optimal concentration of chlorhexidine, the frequency of application, the effect on promoting resistance among oropharyngeal flora, and cost-effectiveness.

**Funding**
Society of Critical Care Medicine, 2006 Vision Grant.

**Bibliographic details**

**PubMedID**
17205028

**DOI**
10.1097/01.CCM.0000253395.70708.AC

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Administration, Topical; Anti-Infective Agents, Local /administration & dosage; Chlorhexidine /administration & dosage; Humans; Pneumonia, Ventilator-Associated /prevention & control; Randomized Controlled Trials as Topic

**AccessionNumber**
12007000540

**Date bibliographic record published**
10/03/2008

**Date abstract record published**
01/09/2008

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.