Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis

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CRD summary
The review found that there was strong evidence that oral antiseptics helped prevent ventilator-associated pneumonia compared to oral care without antiseptics. The review was generally well-conducted and these conclusions appear reliable.

Authors’ objectives
To determine whether oral care with chlorhexidine or povidone-iodine reduced the occurrence of ventilator-associated pneumonia in mechanically-ventilated adults compared with oral care without these antiseptics.

Searching
PubMed, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index, Google Scholar, ClinicalTrials.gov and Current Controlled Trials were searched for articles published in English, French or Dutch from 1975 to February 2011, and for unpublished studies. Search terms were reported. Conference abstracts and the reference lists of relevant articles were also checked for additional studies.

Study selection
Randomised controlled trials (RCTs) of oral care for mechanically ventilated adults that compared use of chlorhexidine or povidone-iodine versus standard oral care, placebo or another product were eligible for inclusion. Studies were required to report ventilator-associated pneumonia. Studies of antibiotics for oral decontamination were excluded.

The intervention in most of the included studies was chlorhexidine (0.12%, 0.2% or 2%), but two studies assessed povidone-iodine (1% or 10%). Interventions differed markedly between studies (where reported) with respect to application method (such as oral rinse, gel, spray, swab, paste), drug concentration, frequency of application, duration of intervention and other oral care techniques used (brushing, suction, rinsing etc). Controls received placebo, saline, potassium permanganate or standard care (which varied considerably across studies). Most studies reported little or no information about methods (other than oral care) used to prevent ventilator-assisted pneumonia. Most studies were set in mixed intensive care units or open heart surgery units. Ventilator-associated pneumonia, which was the only outcome reported in this review, was defined in most studies using United States Centers for Disease Control Prevention definition or similar (where reported). Inclusion and exclusion criteria varied widely across studies, as detailed in the review.

Two reviewers checked titles retrieved by the search, supervised by a third reviewer. Selected abstracts were screened for inclusion independently by four reviewers, with disagreements resolved by consensus.

Assessment of study quality
The following aspects of study quality were assessed using a validated checklist: randomisation; blinding; baseline comparability of groups; losses to follow-up; use of intention-to-treat (ITT) analysis; comparability of treatment; sample size; clear definition of inclusion criteria and outcomes; and overall quality.

Study quality was assessed by two reviewers and checked by a third.

Data extraction
Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated or extracted for each study. For one study with two intervention groups receiving the intervention at differing frequencies, both groups were combined for comparison with controls. Similarly, where studies included more than one eligible control arm, the controls were combined for the purpose of comparison. A group in one RCT who received chlorhexidine with colistin were excluded from analysis. Study authors were contacted for further data if necessary.
The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**

Studies were combined to calculate pooled risk ratios and 95% confidence intervals using a random-effects Mantel-Haenszel model. Statistical heterogeneity was assessed using $I^2$ and was defined as low (25% or less), moderate (25% to 50%) or high (50% or greater). Publication bias was assessed with funnel plots. Subgroup analyses were conducted to investigate the impact of type of antiseptic (chlorhexidine or povidone-iodine), concentration of chlorhexidine (2%, 0.2% or 0.12%), type of intensive care unit (cardiac, fixed, surgery or trauma) and whether blinding was reported.

**Results of the review**

Fourteen RCTs were included in the review (2,481 participants, range five to 561). Nine were blinded and two were double-blinded.

When studies were pooled, oral care with chlorhexidine or povidone-iodine significantly reduced the risk of ventilator-associated pneumonia, with moderate statistical heterogeneity (RR 0.67, 95% CI 0.50 to 0.88; 14 RCTs, 2,481 participants, $I^2=38\%$).

In subgroup analysis by type of antiseptic, chlorhexidine was more effective than controls with moderate heterogeneity (RR 0.72, 95% CI 0.55 to 0.94; 12 RCTs, 2,341 participants, $I^2=29\%$), but there was no statistically significant difference between povidone-iodine and controls, with high heterogeneity (two RCTs, 140 participants, $I^2=69\%$). In subgroup analysis by concentration of chlorhexidine, only the 2% solution was significantly more effective than controls, and heterogeneity was absent (RR 0.53, 95% CI 0.31 to 0.91; two studies, 464 participants, $I^2=0\%$). In subgroup analysis by type of intensive care unit, only cardiac surgery intensive care units were associated with a formally statistically significant risk reduction; again heterogeneity was absent (RR 0.41, 95% CI 0.17 to 0.98; two RCTs, 914 participants, $I^2=0\%$). Subgroup analysis by blinding status was also reported in the review.

No evidence of publication bias was found.

**Authors’ conclusions**

There was strong evidence that oral antiseptics helped prevent ventilator-associated pneumonia compared to oral care without antiseptics.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for published and unpublished studies. Language restriction meant that there was potential for language bias. Formal testing showed no evidence of publication bias. Steps were taken to reduce the risk of reviewer bias and error by having more than one reviewer independently undertake study selection, quality assessment and data extraction. Relevant aspects of quality were assessed but no details were reported about the quality of individual studies.

Appropriate methods were used to combine the studies and assess and explore heterogeneity. As the authors noted, there was strong methodological and clinical heterogeneity between the studies, with moderate or high statistical heterogeneity for some analyses. Evidence that the intervention had differential effects in specific subgroups was rather weak, as all confidence intervals overlapped and some subgroups had very few studies. However, the review was generally well-conducted and the authors’ main conclusions appear reliable.

**Implications of the review for practice and research**

**Practice:** Authors stated that when planning oral care for intubated patients, clinicians should take into account the evidence that oral antiseptics help prevent ventilator-associated pneumonia.

**Research:** Authors stated that larger and standardised comparative studies of povidone-iodine for oral care were needed. Research was also required to determine the effects of frequency of antiseptic application and the effect of tooth-brushing in conjunction with antiseptic use.

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