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RESEARCH

Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis

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ABSTRACT

Objective To evaluate the effect of oral decontamination on the incidence of ventilator associated pneumonia and mortality in mechanically ventilated adults.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, CINAHL, the Cochrane Library, trials registers, reference lists, conference proceedings, and investigators in the specialty.

Review methods Two independent reviewers screened studies for inclusion, assessed trial quality, and extracted data. Eligible trials were randomised controlled trials enrolling mechanically ventilated adults that compared the effects of daily oral application of antibiotics or antiseptics with no prophylaxis.

Results 11 trials totalling 3242 patients met the inclusion criteria. Among four trials with 1098 patients, oral application of antibiotics did not significantly reduce the incidence of ventilator associated pneumonia (relative risk 0.69, 95% confidence interval 0.41 to 1.18). In seven trials with 2144 patients, however, oral application of antiseptics significantly reduced the incidence of ventilator associated pneumonia (0.56, 0.39 to 0.81). When the results of the 11 trials were pooled, rates of ventilator associated pneumonia were lower among patients receiving either method of oral decontamination (0.61, 0.45 to 0.82). Mortality was not influenced by prophylaxis with either antibiotics (0.94, 0.73 to 1.21) or antiseptics (0.96, 0.69 to 1.33) nor was duration of mechanical ventilation or stay in the intensive care unit.

Conclusions Oral decontamination of mechanically ventilated adults using antiseptics is associated with a lower risk of ventilator associated pneumonia. Neither antiseptic nor antibiotic oral decontamination reduced mortality or duration of mechanical ventilation or stay in the intensive care unit.

INTRODUCTION

Ventilator associated pneumonia remains a leading cause of morbidity and mortality among mechanically ventilated patients, with the incidence ranging from 9% to 27% and a crude mortality that may exceed 50%.[1-4] Aspiration of bacteria from the upper digestive tract is important in the pathogenesis of this infection.[4 5] Two different interventions aimed at decreasing the oral bacterial load are selective decontamination of the digestive tract, involving administration of non-absorbable antibiotics by mouth and through a nasogastric tube, and oral decontamination, which is limited to topical oral application of antibiotics or antiseptics.

Previous meta-analyses of selective decontamination of the digestive tract found a significant reduction in rates of ventilator associated pneumonia among treated patients.[6-14] The use of this intervention is, however, limited by concern about the emergence of antibiotic resistant bacteria.[15-17] Oral decontamination alone therefore may be more attractive because it requires only a fraction of the antibiotics used in selective decontamination of the digestive tract. To date, trials of oral decontamination using antibiotics have generated conflicting results, some suggesting benefit[18 19 w1] and others showing no benefit.[w2 w3]

One alternative to oral decontamination with antibiotics is to use antiseptics, such as chlorhexidine gluconate or povidone iodine. In contrast to antibiotics, antiseptics act rapidly at multiple target sites and accordingly may be less prone to induce drug resistance.[20] Observational studies suggest that antiseptic oral decontamination can reduce ventilator associated pneumonia,[21 22] but randomised controlled trials are not convincing.[23 w4-w6] Recently a meta-analysis of four trials on chlorhexidine failed to show a significant reduction in rates of ventilator associated pneumonia.[24] Two subsequent randomised controlled trials, however, suggested benefit from this approach.[w7 w8]

Current guidelines from the Centers for Disease Control and Prevention recommend topical oral chlorhexidine 0.12% during the perioperative period for adults undergoing cardiac surgery (grade II evidence).[3] The routine use of antibiotic or antiseptic oral decontamination for the prevention of ventilator associated pneumonia, however, remains unresolved.[3] Despite the lack of firm evidence favouring this preventive intervention, a recent survey across 59 European intensive care units from five countries showed that 61% of the respondents used oral decontamination with chlorhexidine.[25]

We carried out a systematic review and meta-analysis to estimate the effect of oral decontamination using topical antibiotics or antiseptics on ventilator associated pneumonia and mortality in mechanically ventilated adults.

METHODS

With the assistance of a professional librarian we searched for relevant randomised controlled trials using the Ovid version of Medline (1966 to May week 3, 2006) and a maximally sensitive strategy. We modified this search for Embase (1980 to week 21, 2006) and CINAHL (1982 to May week 3, 2006). We also searched CENTRAL (the Cochrane Central Register of Controlled Trials, the Cochrane Library, issue 1, 2006) and the Cochrane Database of Systematic Reviews, issue 1, 2006. We screened previous meta-analyses and the references lists from all retrieved articles for additional studies. Further searches were carried out in two trials registers (www.clinicaltrials.gov/ and www.controlled-trials.com/) and on the web postings from conference proceedings, abstracts, and poster presentations. We also contacted authors and experts in the specialty.

Study selection and data extraction

We included published and unpublished randomised controlled trials testing the effect of oral decontamination on the incidence of pneumonia and mortality in adults requiring mechanical ventilation in an intensive care unit. We considered any type or combination of antibiotics or antiseptics. We had no language restrictions. Trials on selective decontamination of the digestive tract, observational studies, editorials, and commentaries were excluded.

Two independent reviewers (EC and AR) screened all titles and abstracts for inclusion. One reviewer (AR) was blinded to author, journal, institutional affiliation, and date of publication. We then independently assessed each selected reference for detailed evaluation. Interobserver agreement on the selection of articles for inclusion was measured with Cohen's (unweighted) κ statistic.[26] Two reviewers (EC and AR) also independently abstracted relevant trial characteristics, and disagreements were resolved by discussion. We contacted authors of the primary studies for clarifications as necessary.

Quality assessment

Two reviewers (EC and AR) independently appraised the quality of included trials. We evaluated randomisation, allocation concealment, blinding techniques, clarity of inclusion and exclusion criteria and outcome definitions, similarity of baseline characteristics, and completeness of follow-up. We considered randomisation to be true if the allocation sequence was generated using computer programs, random number tables, or random drawing of opaque envelopes. Alternate treatment allocation was classified as non-random. Allocation was considered concealed if it involved a telephone call to a central site, used opaque sealed envelopes, or was executed centrally by the pharmacy. Allocation was categorised as unconcealed when described as open or directly managed by the study investigators or when the methods were unclear. A study was considered blinded when patients, caregivers, and data collectors or outcome assessors were blinded, or when it was reported as double blind by the authors. We contacted authors to clarify methodology as necessary.

Data synthesis

We grouped trials according to the specified prophylactic agent used for oral decontamination. The two broad categories were randomised controlled trials in which oral antibiotics were tested against no prophylaxis and oral antiseptics were tested against no prophylaxis.

The primary outcomes were incidence of ventilator associated pneumonia and mortality. We used the authors' definition for ventilator associated pneumonia if it included clinical and radiological criteria. As such, we excluded trials that used the clinical pulmonary infection score alone. We considered mortality in the intensive care unit in the absence of hospital mortality data. Secondary outcomes were the group mean duration of mechanical ventilation and stay in the intensive care unit. We also combined trials on antibiotics and antiseptics for the primary outcomes of ventilator associated pneumonia and mortality, in light of the a priori expectation of a similar magnitude and direction of treatment effect.

Meta-analysis was carried out using Review Manager 4.2 (Cochrane Collaboration, Oxford) and a random effects model.[27] The pooled effects estimates for binary variables were expressed as relative risk with 95% confidence interval, whereas continuous variables were expressed as mean differences with 95% confidence intervals. We tested the difference in estimates of treatment effect between the treatment and control groups for each hypothesis using a two sided z test with statistical significance considered at $P<0.05$. We calculated the number of patients needed to treat (NNT, with 95% confidence interval) to prevent one episode of ventilator associated pneumonia during the period of mechanical ventilation, using the formula:

$$NNT=1/(RRR\times\text{median CER})$$

where RRR is the summary relative risk reduction and median CER is the median of the control events rates for all trials.

We used Cochran Q and I^2 statistics to assess for heterogeneity of results.[28,29] We predefined heterogeneity as low, moderate, and high with I^2 of above 25%, 50%, and 75%.[29] The a priori hypotheses to explain heterogeneity were method of allocation (smaller treatment effect in concealed compared with unconcealed allocation), blinding technique (smaller treatment effect in blinded compared with unblinded studies), patient population (smaller treatment effect in medical or mixed patients compared with selected surgical or trauma patients), and duration of ventilation (smaller

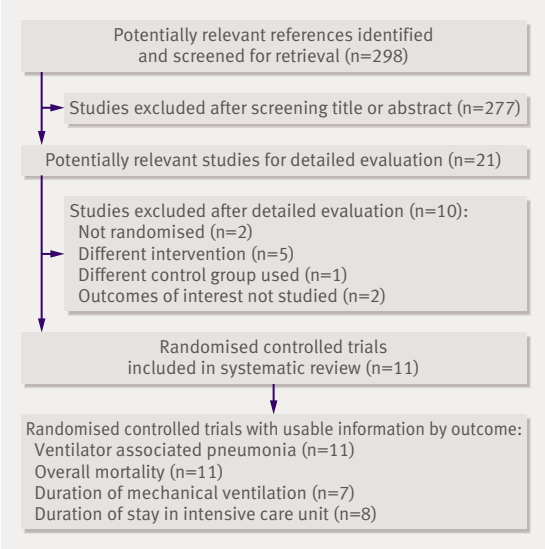

Fig 1 | Flow of studies through trial

treatment effect in patients with mean duration of ventilation of 48 hours or more compared with less than 48 hours). The purpose of the first two analyses was to evaluate whether two critical methodological qualities influenced results.[30] We also carried out a post hoc subgroup analysis to investigate the influence of alternative approaches to the diagnosis of ventilator associated pneumonia (quantitative culture of bronchoalveolar lavage fluid or protected specimen brush compared with non-quantitative culture of endotracheal aspirate or other criteria).

We compared relative risk estimates between subgroups using a two sided z test on the log relative risks, and expressed as a ratio of relative risks with its 95% confidence interval.[31]

The three trials with three arm comparisons were analysed as follows. In two studies,[w1 w8] owing to the similarity of the control arms, we pooled them and compared the results with the treatment group. In the third study[w7] we excluded one of the two control arms from analysis because it incorporated both antibiotics and chlorhexidine.

To evaluate potential publication bias we constructed a funnel plot for the primary outcome of ventilator associated pneumonia, using odds ratio as the measure of effect, and visually inspected it for asymmetry. We also carried out Egger's regression intercept and Begg's rank correlation tests to assess this asymmetry formally. Analysis was done using Comprehensive Meta-analysis version 2.2.040 (Biostat, Englewood, NJ). We considered a one tailed P value of less than 0.05 as significant.

RESULTS

Eleven randomised controlled trials totalling 3242 patients met the inclusion criteria (table 1 and fig 1). Nine were reports published between 1994 and 2006,[w1-w9] and two were published in abstract form.[w10 w11] Four trials (1098 patients) assessed the effectiveness of antibiotic oral decontamination, whereas seven (2144 patients) evaluated the effectiveness of antiseptic oral decontamination. In the antibiotic category one trial tested Iseganan as the decontaminant.[w2] Iseganan is a synthetic variant of a porcine protegrin, which is a natural antibiotic peptide released by neutrophils in response to invasion by microbes. Details of the excluded studies are available on request.[18 19 21 23 32-37]

All included studies were parallel design randomised controlled trials and were published in English. Most included general mixed patients in intensive care. Nine studies compared active treatment with placebo and two[w5 w8] used "standard oral care" as the control. In all trials except five,[w1 w2 w4-w6] the prophylactic regimen was given until extubation. Few studies reported on confounding strategies to prevent ventilator associated pneumonia.[38] Three trials mentioned semirecumbent positioning[w1 w7 w8] and only one trial controlled for route of intubation and management of humidification using a ventilator circuit.[w8]

The diagnostic criteria for ventilator associated pneumonia differed across trials (table 1). Several trials used quantitative microbiology to confirm ventilator associated pneumonia: three[w1 w2 w8] required a quantitative culture of bronchoalveolar lavage fluid or protected specimen brush, two used quantitative cultures of bronchoalveolar lavage fluid or endotracheal aspirate,[w5 w6] and one used quantitative cultures of tracheal aspirates.[w10] The other trials used either semiquantitative techniques[w3 w7 w11] or did not require microbiological confirmation,[w9] whereas in one trial the criteria were unclear.[w4] Except for three trials, the inclusion criteria included an anticipated duration of mechanical ventilation of 48 hours or more. Patients were ventilated for a mean duration of more than 48 hours in all but one trial.[w9] Seven trials reported duration of mechanical ventilation as means and standard deviations; eight trials reported duration of stay in the intensive care unit as such. One trial[w1] reported both of these outcomes as median and range values; these results were not included in the pooled analyses.

Interobserver agreement on the selection of trials for potential inclusion based on reading the titles and abstracts was excellent (Cohen's unweighted κ=0.84, 95% confidence interval 0.64 to 1.03). Interobserver agreement on the inclusion of relevant studies after detailed evaluation was also excellent (κ=1).

Eight of nine authors responded to our requests and provided additional information on trial design, key quality features, and outcome data. Table 2 shows the methodological quality of included trials.

Primary outcomes

Ventilator associated pneumonia

Results from 11 trials (3242 patients) were available to examine the effects of oral decontamination on rates of ventilator associated pneumonia. Meta-analysis of four trials (1098 patients) testing antibiotic oral decontamination did not show a statistically significant reduction

Table 1 | Characteristics of included trials

Study	Population	Intervention	Comparison	Outcomes	Follow-up	Funding
Bergmans 2001[w1]	Mixed	Orabase with gentamicin, colistin, and vancomycin, 4 times daily until extubation, death, limited to 21 days	Control A, placebo in intensive care unit with patients receiving topical antimicrobial prophylaxis; control B, placebo in intensive care unit with no topical antimicrobial prophylaxis	Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations, including quantitative culture of bronchoalveolar lavage fluid or protected specimen brush. Mortality in hospital	Until extubation or death	Local and industry
De Riso 1996[w4]	Cardiothoracic (open heart surgery)	Chlorhexidine 0.12% 15 ml preoperatively and twice daily postoperatively until discharge from intensive care or death	Placebo	Ventilator associated pneumonia: Centers for Disease Control and Prevention criteria.‡ Mortality in hospital	Until discharge from intensive care unit or death	Local
Fourrier 2000[w5]*	Medical or surgical	Chlorhexidine 0.2% gel three times daily during stay in intensive care unit until 28 days, discharge from intensive care, or death	Standard treatment	Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations and quantitative culture of tracheal aspirate or bronchoalveolar lavage fluid, or both. Mortality in intensive care unit	Until discharge from intensive care unit or death	Local
Fourrier 2005[w6]*†	60% medical, 40% surgical	Chlorhexidine 0.2% gel three times daily during stay in intensive care unit until 28 days	Placebo	Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations and quantitative culture of tracheal aspirate or bronchoalveolar lavage fluid, or both. Mortality in intensive care unit by day 28	Until 28 days in intensive care, discharge from intensive care unit, or death	Local, and industry provided study drug
Koeman 2006[w7]*	Mixed	Treatment A, chlorhexidine 2% in white petroleum vehicle four times daily until diagnosis of ventilator associated pneumonia, death, or extubation; treatment B, chlorhexidine 2% and colistin four times daily	Placebo	Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations and semiquantitative culture of tracheal aspirates. Independent adjudication committee determined if patients had ventilator associated pneumonia. Mortality in intensive care unit	Until extubation, discharge from intensive care unit, or death	Local
Kollef 2006[w2]†	83% non-trauma, 27% trauma	Iseganan 3 ml (9 mg) six times daily until 14 days. Treatment discontinued if patient developed ventilator associated pneumonia or was extubated	Placebo	Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations, including quantitative culture of bronchoalveolar lavage fluid or non-directed bronchoalveolar lavage fluid. Mortality in intensive care unit by day 14	Until 21 days or death	Industry
Laggner 1994[w3]	General intensive care	Gentamicin gel four times daily until extubation. All received oral amphotericin B and oral disinfection with phenylhydragyrum boricum and hexetidine	Placebo	Ventilator associated pneumonia: clinical and radiological investigations and positive culture of tracheal secretions. Mortality in intensive care unit	Until extubation	Not reported
MacNaughton 2004[w11]*	Medical or surgical	Chlorhexidine 0.2% oral rinse twice daily until extubation or death	Placebo	Ventilator associated pneumonia: leucocytosis and pyrexia >38°C; deterioration in arterial blood gases; chest signs; new consolidation on chest radiography; and significant semiquantitative culture of non-directed bronchoalveolar lavage fluid. Definite pneumonia 4/4 if met all four criteria. Mortality in intensive care unit	Not available	Local
Rios 2005[w10]*	Medical or surgical (including trauma)	Polymyxin B and gentamicin gel three times daily until 24 hours after extubation	Placebo	Ventilator associated pneumonia: clinical, radiological, and bacteriological, including positive quantitative culture of tracheal secretions. Mortality in intensive care unit	Until 28 days after ventilator associated pneumonia diagnosis or discharge from intensive care unit, or hospital discharge	Local
Segers 2005[w9]*	Cardiothoracic	Chlorhexidine 0.12%, nasal ointment, and 10 ml oropharynx rinse four times daily on allocation and admission to hospital until extubation or removal of nasogastric tube	Placebo	Ventilator associated pneumonia: Centers for Disease Control and Prevention criteria (no microbiological confirmation required). Mortality in hospital	Until 48 hours after discharge	Local
Seguin 2006[w8]*	Surgical (severe closed head trauma)	Povidone iodine 10% 20 ml reconstituted to 60 ml with sterile water to nasopharynx and oropharynx six times daily until extubation	Control A, saline rinse 60 ml; control B, standard treatment	Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations including positive quantitative culture of bronchoalveolar lavage fluid or non-directed bronchoalveolar lavage fluid. Mortality in intensive care unit	Until discharge from intensive care unit	Not funded

*Published and unpublished data.
†Trial stopped early.
‡Unclear if clinically defined ventilator associated pneumonia or microbiology confirmed ventilator associated pneumonia.

in ventilator associated pneumonia rates (relative risk 0.69, 0.41 to 1.18; P=0.18; I^2=59.4%; fig 2). Pooled analysis of the seven trials (2144 patients) that tested the effect of antiseptic oral decontamination on ventilator associated pneumonia showed a significant reduction (relative risk 0.56, 0.39 to 0.81; P=0.002; I^2=48.2%). The 11 trials combined favoured oral decontamination (relative risk 0.61, 0.45 to 0.82; P<0.001; I^2=52.5%). Fourteen patients (NNT 14, 10 to 31) would need to receive oral decontamination with one of these methods to prevent one case of ventilator associated pneumonia.

Table 3 summarises the four a priori subgroup analyses. An informative comparison was possible for only two subgroups in the antiseptic trials, because either none or one comparison group existed for the other subgroups. Blinded trials yielded a more modest treatment effect than unblinded trials; medical or mixed populations also seemed to derive a more modest treatment effect compared with surgical or trauma patients. Table 3 also shows the post hoc subgroup analyses on diagnostic criteria for ventilator associated pneumonia where it was possible to compare the subgroups only in the antibiotics trials. Trials that used quantitative culture of bronchoalveolar lavage fluid observed a trend towards greater treatment effects compared with those that relied on less invasive diagnostic methods.

Overall mortality

Results of all 11 trials were available for the analysis of mortality (fig 3). Meta-analysis of the four trials that tested antibiotic prophylaxis found no effect on overall mortality (relative risk 0.94, 0.73 to 1.21; P=0.63; I^2=34.8%). The pooled analysis of the seven antiseptic trials (2144 patients) also showed no effect on mortality (0.96, 0.69 to 1.33; P=0.82; I^2=42.7%). Pooling the 11 studies produced similar results (0.97, 0.80 to 1.18; P=0.74; I^2=34.3%).

Duration of mechanical ventilation

Overall seven trials (1760 patients) contributed to the analysis of duration of mechanical ventilation. Neither the pooled mean difference for prophylaxis using

Table 2 | **Methodological quality of included trials**

Study	Randomisation	Allocation concealment	Blinding	Explicit inclusion and exclusion criteria	Baseline similarities‡	% Patients analysed for ventilator associated pneumonia divided by total No of patients randomised	Exclusions after randomisation
Bergmans[w1]	Unclear	Executed by pharmacy	Described as double blind	Yes	Yes	92.2	Early extubation or death (‹48 hours)
De Riso[w4]	Computer generated list	Executed by pharmacy	Patients, caregivers, outcome assessors	Yes	Yes	Presumably 100	Not available
Fourrier[w5]*	Computer generated list, randomisation in block of 4	Unclear	Described as single blind	Yes	Yes	Presumably 100	Not available
Fourrier[w6]*	Block randomisation stratified by site	Sealed envelopes by pharmacy	Described as double blind	Yes	Yes	99.6	Protocol violation: oral topical antibiotherapy needed
Koeman[w7]*	Computer randomised tables stratified by centre	Executed by pharmacy	Patients, caregivers, data collectors, outcome assessors	Yes	Yes	100	None
Kollef[w2]	Computer generated list	Central telephone	Patients, caregivers, data collectors, outcome assessors	Yes	Yes	97.8 (only 87.7 completed the study. Unclear if those withdrawn, missing, or lost to follow-up were evaluated for ventilator associated pneumonia)	Did not receive study drug
Laggner[w3]	Computer generated randomisation in time blocks†	Open	Described as double blind	Yes	Yes	76.1	Early extubation (‹ 5 days), enteral nutrition
Macnaughton[w11]*	Block randomisation by random table	Executed by pharmacy	Described as double blind (patients, caregivers, investigators)	Yes	Unclear	100	None
Rios[w10]*	Random opening of opaque envelopes	Executed by pharmacy	Patients, caregivers, data collectors, outcome assessors	Yes	Yes	82.8	Decision to limit therapeutic efforts, death, or early extubation
Segers[w9]*	Computer randomised list	Executed by pharmacy	Patients, caregivers, data collectors, outcome assessors	Yes	Yes	96.3	Selective decontamination of digestive tract, withdrew consent, surgery cancelled or death before surgery
Seguin[w8]*	Computer randomised list	Sealed envelopes	Data collectors, outcome assessors	Yes	Yes	89.1	Brain death, early extubation

*Published and unpublished data.
†Information obtained from Liberati et al.[14]
‡Age, sex, severity of disease, and, where available, systemic antibiotic treatment and ulcer prophylaxis usage.

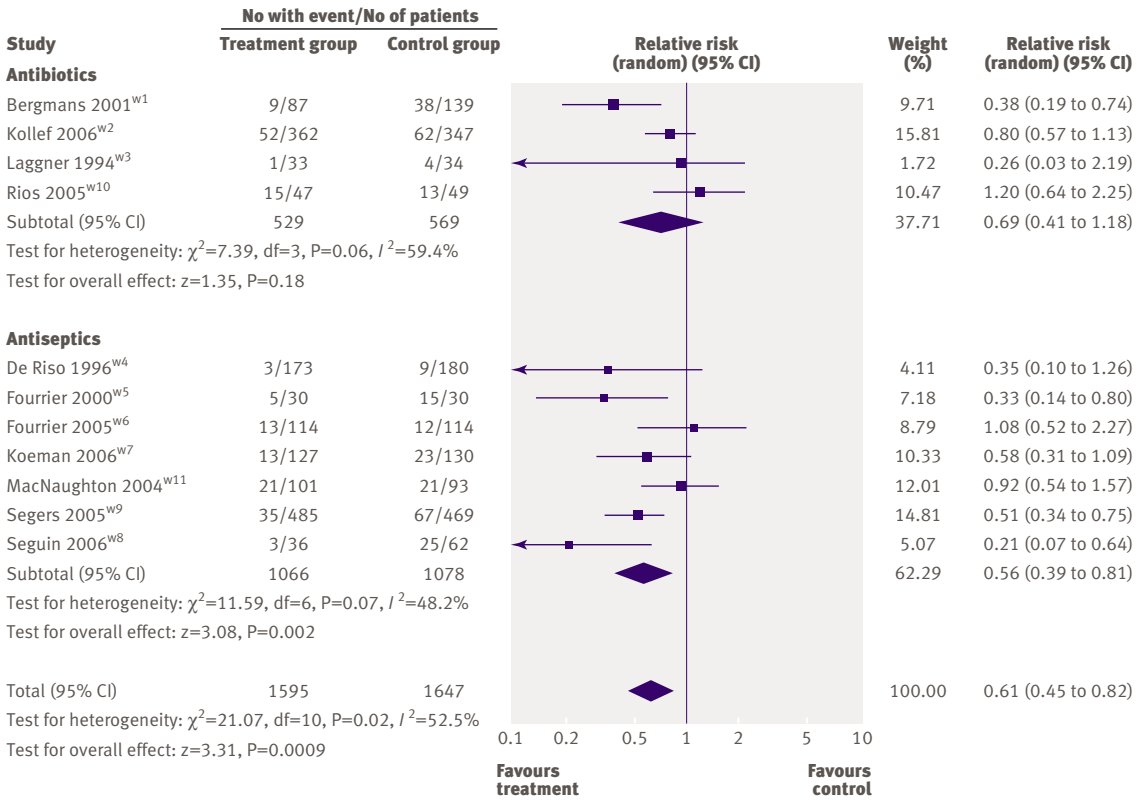

Fig 2 | **Forest plot showing effect of oral decontamination prophylaxis compared with no prophylaxis on risk of ventilator associated pneumonia**

antibiotics (−4.02 days, −9.43 to 1.40; P=0.15; I^2=0%) or antiseptics (0.24 days, −1.01 to 1.48; P=0.71; I^2=40.4%) showed an effect on duration of mechanical ventilation. The combined mean difference for all trials was 0.04 days (−1.15 to 1.23; P=0.95; I^2=31.6%; fig 4).

Duration of stay in intensive care unit

Overall eight trials (2113 patients) contributed to the analysis of the duration of stay in the intensive care unit, which did not seem to be influenced by prophylaxis using either antibiotics (2.30 days,−4.10 to 8.69; P=0.48; I^2=0%) or antiseptics (−0.30 days, −0.78 to 0.19; P=0.23; I^2=83.5%). The combined mean difference for all trials was −0.28 days (−0.76 to 0.19; P=0.24; I^2=77.8%; fig 4).

Publication bias

The funnel plot for ventilator associated pneumonia was asymmetrical, suggesting the existence of unpublished small studies with negative findings (fig 5). Formal statistical tests did not, however, support the presence of publication bias: Egger's regression intercept (intercept −1.32, −3.59 to 0.95; one tailed P=0.111) and Begg's rank correlation (Kendall's τ with continuity correction −0.22; one tailed P=0.175).

DISCUSSION

The effectiveness of prophylactic oral decontamination to prevent pneumonia in patients undergoing mechanical ventilation has remained controversial since its introduction, due partly to discordant results of individual trials. We analysed antibiotic and antiseptic prophylaxis as two distinct approaches to oral decontamination. Our results suggest that antiseptic oral decontamination is effective at preventing ventilator associated pneumonia. More evidence is needed before firm conclusions can be made about antibiotic oral decontamination, although effects may be similar. This review included twice as many participants in the antiseptic trials than antibiotic trials, reflecting more precise results for the analysis of antiseptics.

We found that neither antibiotic nor antiseptic oral decontamination influenced overall mortality, duration of mechanical ventilation, or duration of stay in an intensive care unit. Our review was underpowered to detect any effect on mortality, and the small sample size limited the interpretation of the secondary outcomes.

Comparison with previous studies

Previous meta-analyses examining the effect of prophylaxis using selective decontamination of the digestive tract reported a significant reduction in the incidence of ventilator associated pneumonia.[6-14] The most recent meta-analysis indicated that such an intervention combined with prophylactic intravenous antibiotics reduces overall mortality.[14] In comparison our review suggests that oral antiseptic prophylaxis alone

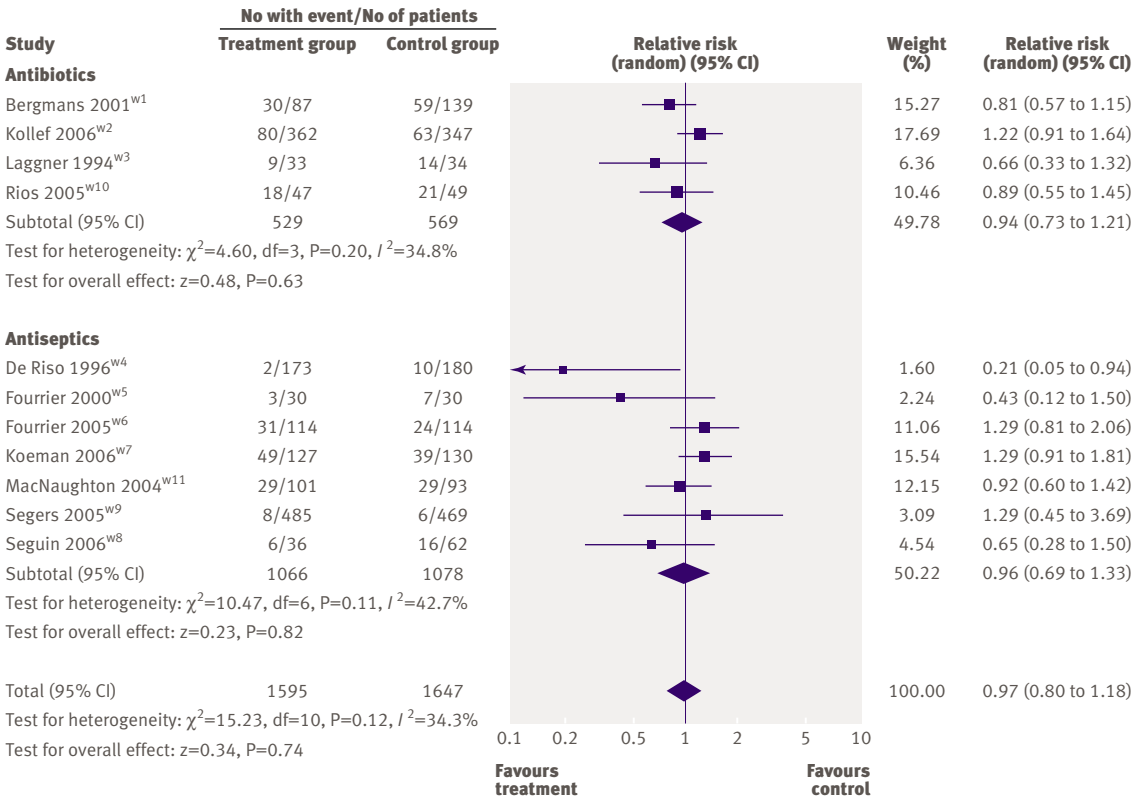

Fig 3 | **Forest plot showing effect of oral decontamination prophylaxis compared with no prophylaxis on overall mortality**

can significantly reduce the incidence of ventilator associated pneumonia, but not mortality. Our meta-analysis on antiseptics differs from the findings of Pineda et al, who pooled four trials on chlorhexidine and did not report lower rates of ventilator associated pneumonia (odds ratio 0.42, 0.16-1.06; P=0.07).[24] Our results also extend those of Chlebicki et al, who did not find a statistically significant benefit using the more conservative random effects model after pooling seven trials on chlorhexidine (relative risk 0.70, 0.47-1.04; P=0.07), although their results were significant with the fixed effects model.[39] Our systematic review included a larger dataset with two more recent trials,[w8 w9] involved clarification of data from several authors, and explored heterogeneity with more subgroup analyses.

Possible explanations and implications

The lack of effect on secondary outcomes may raise concern about the accuracy with which ventilator associated pneumonia was diagnosed, given that the antiseptic trials, despite showing a substantial reduction in ventilator associated pneumonia rates, failed to show similar benefit for these secondary outcomes. It is possible that the combination of clinical, radiological, and microbiological criteria without the use of quantitative investigations using cultures of bronchoalveolar lavage fluid, which may have a high sensitivity but low specificity,[40] may contribute to an overestimation of the ventilator associated pneumonia rates in these trials, and a greater observed treatment effect.

To ensure that the lack of effect on patients' secondary outcomes did not arise from the differences in the diagnostic criteria used by the primary trials, we carried out a post hoc subgroup analysis on the basis of diagnostic criteria for ventilator associated pneumonia (differentiating between trials using invasive quantitative culture of bronchoalveolar lavage fluid or protected specimen brush versus other less invasive approaches). Only one of the antiseptic trials used invasive quantitative criteria, rendering further analysis not possible. Our analysis for the antibiotic trials was inconclusive, showing a trend towards a greater treatment effect for the trials that used the more invasive diagnostic criteria (table 3). An analysis combining all trials on antibiotics and antiseptics also suggested the same trend (invasive quantitative criteria's relative risk 0.45, 0.21 to 0.98 *v* less invasive criteria's relative risk 0.66, 0.47 to 0.93), although the comparison of these relative risks was not conclusive (ratio of relative risks 0.68, 0.29 to 1.58; P=0.37). Nevertheless, a recent large multicentre trial found no difference in clinical outcomes or subsequent overall antibiotic use when a diagnostic approach of quantitative culture of bronchoalveolar lavage fluid was compared with non-quantitative culture of endotracheal aspirate among non-immunocompromised patients not suspected of harbouring high risk organisms.[41]

Our a priori subgroup analyses suggest that trials with an unblinded design and those enrolling surgical or trauma patients tended to yield qualitatively larger treatment effects than blinded trials and those enrolling medical or mixed critically ill patients. The former result is consistent with previous work showing that trials of lower methodological quality tend to report greater treatment effects.[42] Specific surgical or trauma patients often have fewer comorbidities than medical or mixed patients, which may explain the trend towards a greater treatment effect in the former population. However, these subgroup results are best viewed as hypothesis generating.

The finding that antiseptic oral decontamination can reduce the incidence of ventilator associated pneumonia could have important implications for lower healthcare costs and a reduced risk of antibiotic resistance compared with the use of antibiotics. It may not be prudent to adopt this practice routinely for all critically ill patients until strong data on the long term risk of selecting antiseptic and antibiotic resistant organisms are available. Nevertheless, antiseptic oral decontamination seems promising.

Strengths and weaknesses of the study

The strengths of this review include the comprehensive search for relevant randomised controlled trials, duplicate screening, selection, assessment of methodological quality and data abstraction, and use of the random effects model (which takes heterogeneity into account) to combine trial results. We separated and then combined the antibiotic and antiseptic trials, anticipating that the underlying pathophysiology could lead to a similar treatment effect across the trials,[43] and because an overall treatment effect is of interest in examining the relation between oral flora and lung infection during critical illness.

We inspected funnel plots to evaluate potential publication bias for ventilator associated pneumonia. We also undertook formal statistical tests. These did not show the presence of publication bias for the combined 11 antibiotics and antiseptic trials. However, the power of these tests is generally low. Although our literature search was comprehensive, it is possible that we missed other relevant trials. In addition, these trials were heterogeneous with respect to populations enrolled, regimens used, outcome definitions, and analysis strategies, contributing to differing relative risks across the trials. Other limitations of the trials we included were exclusions after randomisation, mainly due to early extubation, early deaths, or protocol violations. Some trials did not explicitly report whether the number of patients analysed reflected the total number of patients randomised (table 2) such that we were unable to abstract the intention to treat analyses from all trials. Finally, we could not obtain unpublished data from some authors on the mean duration of mechanical ventilation and stay in an intensive care unit.

Unanswered questions and future research

Our systematic review supports the use of antiseptic oral decontamination. Research to date does not

Table 3 | Subgroup analyses comparing effect of oral decontamination using antibiotic or antiseptic with no prophylaxis on incidence of ventilator associated pneumonia

	Antibiotic oral decontamination			Antiseptic oral decontamination		
Measurement	Relative risk (95% CI)	No of studies (No of patients)	Ratio of relative risks (95% CI), P value*	Relative risk (95% CI)	No of studies (No of patients)	Ratio of relative risks (95% CI); P value*
Allocation:						
Concealed†	0.73 (0.42 to 1.28)	3 (1031)	—	0.60 (0.40 to 0.89)	6 (2084)	—
Unconcealed	0.26 (0.03 to 2.19)	1 (67)		0.33 (0.14 to 0.80)	1 (60)	
Blinding:						
Blinded‡	—	—	NA§	0.66 (0.47 to 0.93)	5 (1986)	2.36 (1.09 to 5.10); 0.03
Unblinded	—	—		0.28 (0.14 to 0.56)	2 (158)	
Patient population:						
Medical or mixed	—	—	NA¶	0.70 (0.44 to 1.10)	4 (739)	1.67 (0.86 to 3.22); 0.13
Selected surgical or trauma	—	—		0.42 (0.26 to 0.67)	3 (1405)	
Duration of ventilation (hours):						
≥48	—	—	NA**	0.56 (0.34 to 0.91)	6 (1190)	—
<48	—	—		0.51 (0.34 to 0.75)	1 (954)	
Ventilator associated pneumonia diagnostic criteria:						—
Quantitative culture of bronchoalveolar lavage fluid	0.58 (0.28 to 1.22)	2 (935)	0.74 (0.16 to 3.53); P=0.71	0.21 (0.07 to 0.64)	1 (98)	—
Non-quantitative culture of aspirate or others	0.78 (0.20 to 3.12)	2 (163)		0.61 (0.44 to 0.86)	6 (2046)	

*Comparison of estimates in each subgroup (for example, concealed versus unconcealed trials).
†Concealed = reported as open, or unclear.
‡Patients, caregivers, and data collectors or outcome assessors blinded, or reported as double blind.
§None were unblinded.
¶None were surgical or trauma patients.
**None were ventilated for <48 hours.

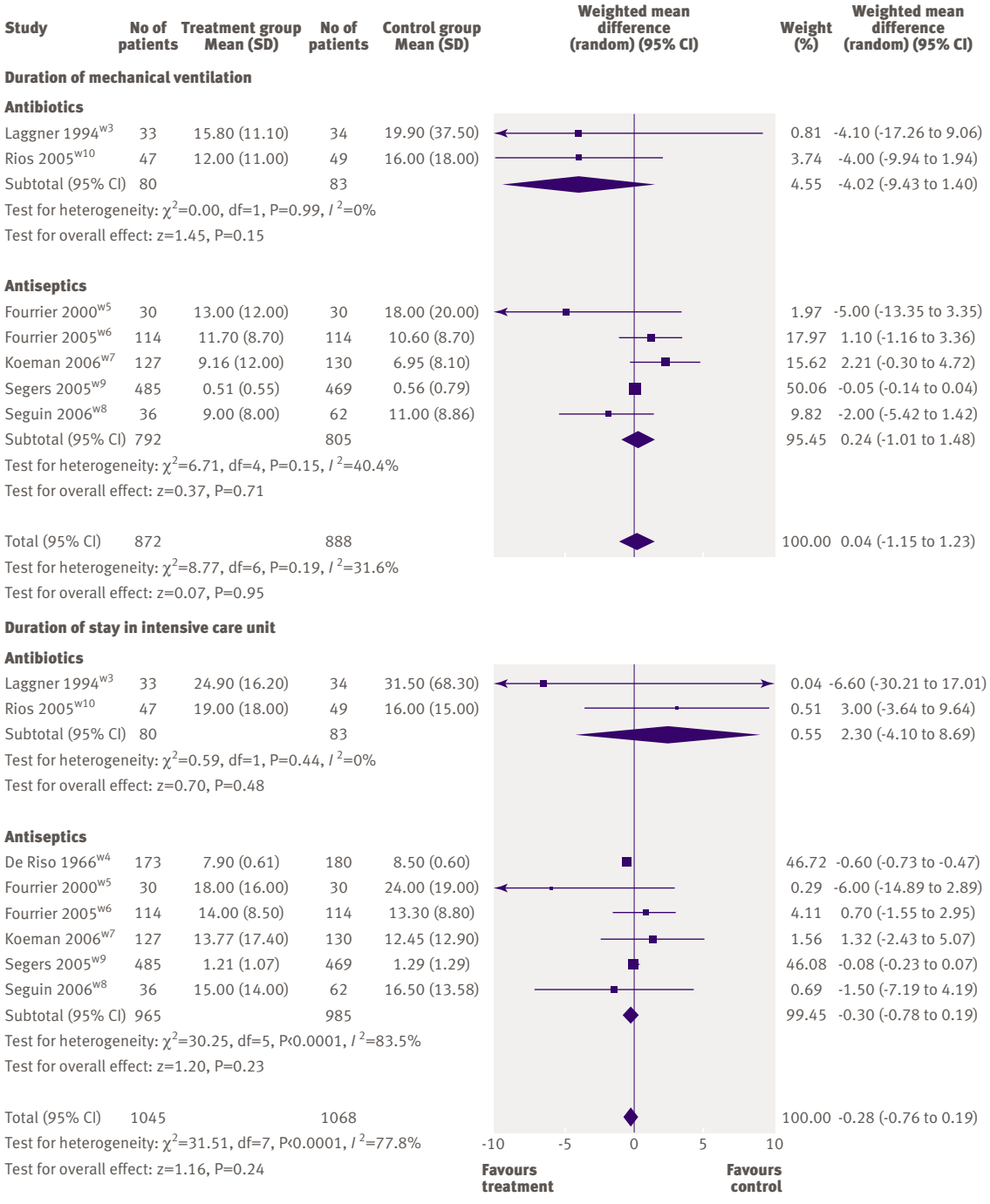

Fig 4 | **Forest plot showing effect of oral decontamination prophylaxis compared with no prophylaxis on duration (days) of mechanical ventilation and duration of stay (days) in an intensive care unit**

address which antiseptic is preferred, since all but one trial evaluated chlorhexidine. We cannot recommend precise methods for chlorhexidine administration owing to the wide variation of treatment regimens among studies. These included varying concentrations (0.12%, 0.2%, 2%), sites of application, forms of agent (oral rinse, gel), and frequencies and techniques of application. Nevertheless, our findings suggest that the concentration of chlorhexidine may be a consideration. In trials with cardiac surgery patients at low risk for developing ventilator associated pneumonia owing to a short duration of intubation, chlorhexidine 0.12% was effective in reducing ventilator associated pneumonia.[w4 w9] However, among medical or mixed intensive care populations, a higher concentration may be necessary. Chlorhexidine was not effective in most of these trials at 0.2% concentration[w6 w11] but was effective at 2%.[w7] As for the only trial that used povidone iodine, the agent was found to be effective in preventing ventilator associated pneumonia among 98

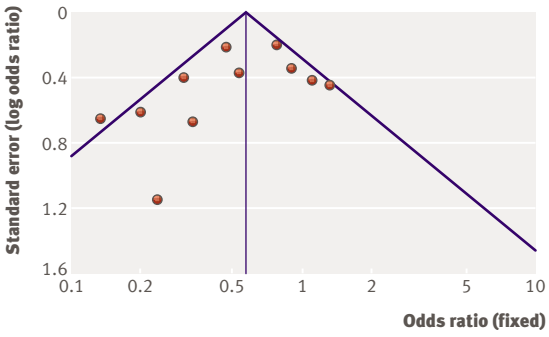

Fig 5 | Funnel plots assessing publication bias for ventilator associated pneumonia

patients with head injuries with a persistent score of 8 or less on the Glasgow coma scale requiring mechanical ventilation for 48 hours or more.[w8]

To our knowledge no trial directly compares antiseptic with antibiotic oral decontamination. Further investigations comparing antibiotic with antiseptic oral decontamination while incorporating stringent infection surveillance would be worthwhile. Whether either antibiotic or antiseptic oral decontamination favourably influence important patient outcomes such as duration of mechanical ventilation or duration of stay in the intensive care unit should be evaluated in rigorously designed and adequately powered randomised trials.

CONCLUSIONS

This systematic review suggests that in mechanically ventilated patients, antiseptic oral decontamination prophylaxis reduces the incidence of ventilator associated pneumonia. More evidence is needed before firm conclusions can be made on the effect of antibiotic oral decontamination. These results should be interpreted in light of the moderate heterogeneity of trial results and possible publication bias. Neither of these two approaches to decontamination seems to affect mortality, duration of mechanical ventilation, or stay in the intensive care unit, although these trials are underpowered for these latter outcomes, and the summary of trials to date does not yet represent the optimum information size.[44] Therefore more evidence is needed before firm conclusions can be made on the full effect of oral decontamination using antiseptics and, particularly, antibiotics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Selective decontamination of the digestive tract reduces the incidence of ventilator associated pneumonia

Oral decontamination requires only a fraction of the antibiotics used for selective decontamination

WHAT THIS STUDY ADDS

Oral decontamination using antiseptics reduces the incidence of ventilator associated pneumonia

Neither antibiotic nor antiseptic oral decontamination reduces overall mortality or duration of mechanical ventilation or stay in intensive care

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