

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. Aspiration of bacteria from the upper digestive tract is important in this infection.^{1,2} Interventions aimed at decreasing the bacterial load are selective decontamination of the digestive tract (non-absorbable antibiotics by mouth and nasogastric tube) and oral decontamination (topical antibiotics or antiseptics). Oral decontamination requires only a fraction of the antibiotics used for selective decontamination, reducing the risk of antibiotic resistant bacteria. Antiseptics such as chlorhexidine gluconate could be used as an alternative to antibiotics as they may be less prone to induce drug resistance.³ Observational studies

suggest that antiseptics can reduce ventilator associated pneumonia,^{4,5} but randomised controlled trials are not convincing.^{6 w4-w6}

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

METHODS

We searched for randomised controlled trials testing the effect of oral decontamination on the incidence of pneumonia and mortality in mechanically ventilated adults (see bmj.com). 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 (see bmj.com). We grouped trials into two categories: antibiotics compared with no prophylaxis and antiseptics compared with no prophylaxis. The primary outcomes were incidence of ventilator associated pneumonia and mortality. Secondary outcomes were the group mean duration of ventilation and stay in intensive care. We also combined trials for the primary outcomes.

Meta-analysis was carried out using RevMan 4.2 and a random effects model.⁷ Pooled effects estimates for binary variables were expressed as relative risk (95% confidence interval) and continuous variables as mean differences (95% confidence intervals). We tested the difference in estimates of treatment effect between treatment and control groups for each hypothesis using a two sided z test, considered significant 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 (see formula on bmj.com).

We used Cochran Q and I² statistics to assess heterogeneity.^{8,9} We predefined heterogeneity as low (I² > 25%), moderate (> 50%), and high (75%).⁹ The a priori hypotheses to explain heterogeneity were method of allocation (concealed v unconcealed), blinding technique (blinded v unblinded), patient population (medical or mixed v selected surgical or trauma), and mean duration of ventilation (≥ 48 hours v < 48 hours). We 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 v non-quantitative culture of endotracheal aspirate or other criteria).

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We compared relative risks between subgroups using a two sided z test on the log relative risks, expressed as a ratio of relative risks (95% confidence interval).¹⁰

Three trials had three arms. In two trials^{w1 w8} we pooled the control arms because of their similarity and compared the results with the treatment group. In the third trial^{w7} we excluded one arm that used antibiotics and chlorhexidine.

We constructed a funnel plot for the primary outcome to look for publication bias and we used Egger's and Begg's tests to assess asymmetry. We considered a one tailed P value of less than 0.05 as significant.

RESULTS

Eleven randomised controlled trials (3242 patients) met the inclusion criteria (see bmj.com). Four (1098 patients) assessed oral decontamination using antibiotics and seven (2144 patients) using antiseptics.

Most of the studies included mixed patients. Nine 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} prophylaxis was given until extubation. Details of the methodological quality of the trials are on bmj.com.

The diagnostic criteria for ventilator associated pneumonia differed across trials (see bmj.com).

Patients were ventilated for a mean duration of more than 48 hours in all but one trial.^{w9}

Meta-analysis of four trials (1098 patients) testing antibiotics did not show a statistically significant reduction in ventilator associated pneumonia rates (relative risk 0.69, 0.41 to 1.18; P=0.18; I²=59%; fig 1). Pooled analysis of seven trials (2144 patients) testing antiseptics showed a significant reduction (0.56, 0.39 to 0.81; P=0.002; I²=48%). The 11 trials combined favoured oral decontamination (0.61, 0.45 to 0.82; P<0.001; I²=53%). Fourteen patients (NNT 14, 10 to 31) would need to receive oral decontamination to prevent one case of ventilator associated pneumonia.

Table 3 on bmj.com details the four subgroup analyses. A comparison was possible for only two subgroups in the antiseptic trials. Blinded trials yielded a more modest treatment effect than unblinded trials as did medical or mixed populations compared with surgical or trauma patients. Trials using quantitative culture of bronchoalveolar lavage fluid observed a trend towards greater treatment effects compared with those using less invasive methods (see bmj.com).

Meta-analysis of the four trials testing antibiotics found no effect on overall mortality (relative risk 0.94, 0.73 to 1.21; P=0.63; I²=35%; fig 2). Pooled analysis of the seven antiseptic trials (2144 patients)

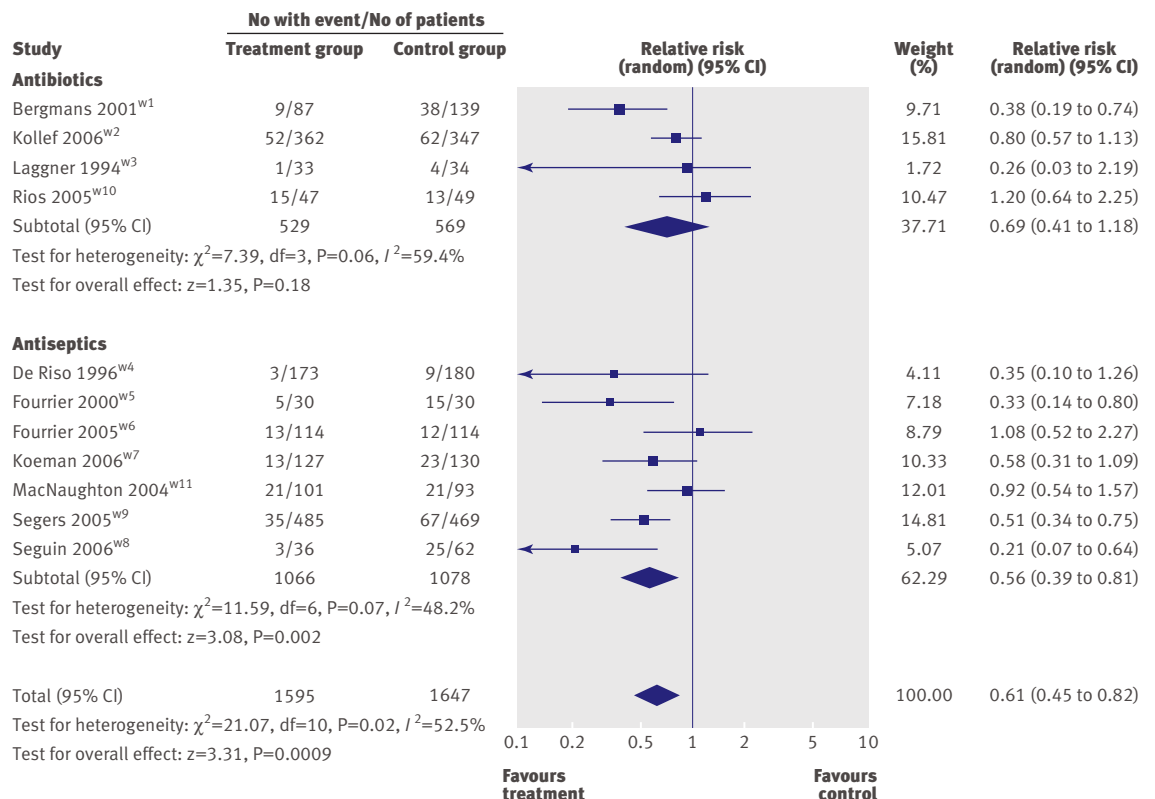


Fig 1 Forest plot showing effect of oral decontamination prophylaxis compared with no prophylaxis on risk of ventilator associated pneumonia

also showed no effect (0.96, 0.69 to 1.33; $P=0.82$; $I^2=43\%$; fig 2). The 11 studies pooled produced similar results (0.97, 0.80 to 1.18; $P=0.74$; $I^2=34\%$).

Seven trials (1760 patients) contributed to the analysis of duration of ventilation. Neither the pooled mean difference for prophylaxis using 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; $P=0.71$; $I^2=40\%$) showed an effect on duration of mechanical ventilation (combined mean difference 0.04 days, -1.15 to 1.23; $P=0.95$; $I^2=32\%$; fig 3).

Eight trials (2113 patients) contributed to the analysis of duration of stay in intensive care, which did not seem to be influenced by prophylaxis using 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; $P=0.23$; $I^2=84\%$). The combined mean difference was -0.28 days (-0.76 to 0.19; $P=0.24$; $I^2=78\%$; fig 3).

The funnel plot was asymmetrical, suggesting the existence of unpublished small studies with negative findings (see bmj.com), but this was not supported by formal tests (see bmj.com).

DISCUSSION

Using antiseptics for oral decontamination of mechanically ventilated adults is effective at preventing ventilator associated pneumonia. More evidence is needed for antibiotics. This systematic review included twice as many participants in the antiseptic

than antibiotic trials, reflecting more precise results for antiseptics.

Neither agent influenced overall mortality or duration of ventilation or stay in intensive care. Our review was underpowered to detect effects on mortality, and the small sample size limited the interpretation of the secondary outcomes.

Meta-analyses examining selective decontamination of the digestive tract reported a significant reduction in ventilator associated pneumonia rates,¹¹⁻¹⁹ whereas a recent meta-analysis indicated that this intervention combined with intravenous antibiotics reduces overall mortality.¹⁹ Our review suggests that antiseptics alone can significantly reduce the incidence of ventilator associated pneumonia, but not mortality.

The lack of effect on secondary outcomes may raise concern about the accuracy of ventilator associated pneumonia diagnosis, given that the antiseptic trials, despite showing a substantial reduction in pneumonia rates, failed to show similar benefit for these secondary outcomes. It is possible that the combination of clinical, radiological, and microbiological criteria without quantitative investigations of bronchoalveolar lavage fluid has low specificity²⁰ and may contribute to an overestimation of the rates in these trials, and a greater observed treatment effect. To take into account differences in diagnostic criteria used by

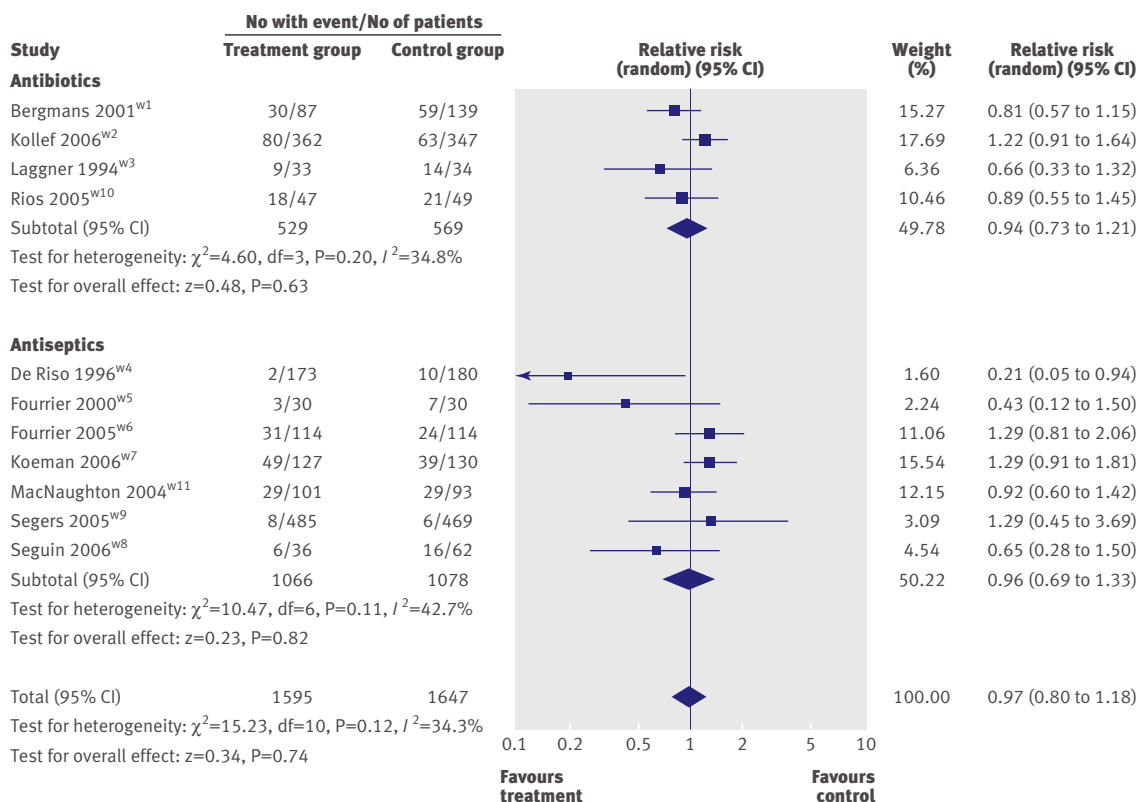


Fig 2 | Forest plot showing effect of oral decontamination prophylaxis compared with no prophylaxis on overall mortality

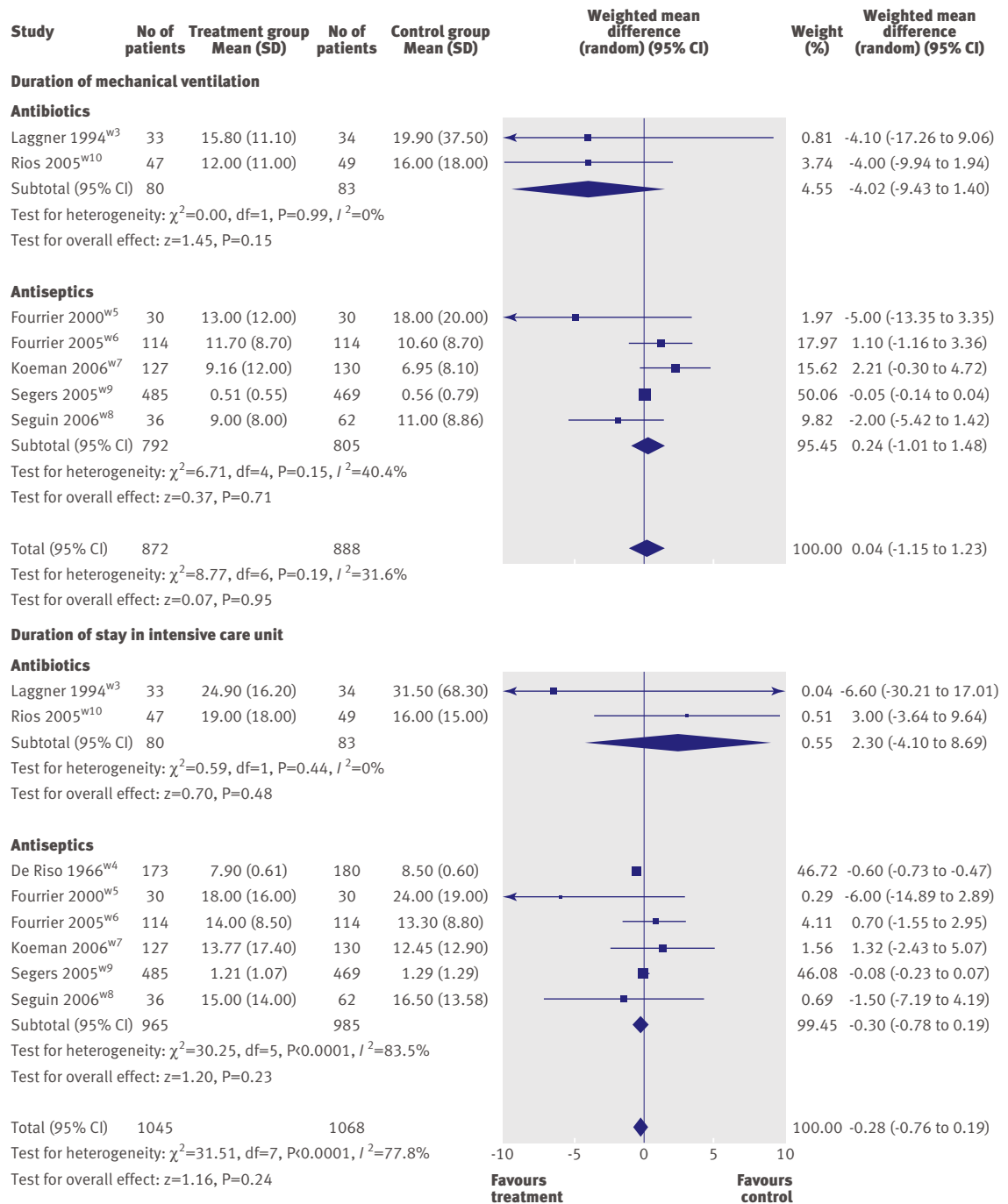


Fig 3 | Forest plot showing effect of oral decontamination prophylaxis compared with no prophylaxis on duration (days) of mechanical ventilation and duration of stay (days) in an intensive care unit

the primary trials, we carried out a post hoc subgroup analysis on the basis of diagnostic criteria. Only one of the antiseptic trials used invasive quantitative criteria. Our analysis for the antibiotic trials was inconclusive, showing a trend towards a greater treatment effect for trials using more invasive criteria (see bmj.com). An analysis of all trials combined suggested the same trend, although the

comparison was not conclusive. Nevertheless, a large multicentre trial found no difference in clinical outcomes or subsequent overall antibiotic use when quantitative culture of bronchoalveolar lavage fluid was compared with non-quantitative culture of endotracheal aspirate among patients not suspected of harbouring high risk organisms.²¹

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

Our subgroup analyses suggest that unblinded trials and those enrolling surgical or trauma patients tended to yield larger treatment effects than blinded trials and those enrolling medical or mixed critically ill patients. Surgical or trauma patients often have fewer comorbidities than medical or mixed patients, which may explain the trend.

The strengths of this review include the comprehensive search, duplicate screening, selection, assessment of methodological quality and data abstraction, and use of the random effects model. We separated and then combined antibiotic and antiseptic trials, anticipating that the underlying pathophysiology could lead to a similar treatment effect across the trials,²² and because an overall treatment effect is of interest in the relation between oral flora and lung infection during critical illness.

We inspected funnel plots and used formal statistical tests for publication bias. These did not show the presence of publication bias for the combined trials. In addition, the trials were heterogeneous for populations, regimens, outcome definitions, and analyses. Other limitations were exclusions after randomisation. Some trials did not explicitly report whether the number of patients analysed reflected the number randomised (see bmj.com) so we were unable to abstract intention to treat analyses from all trials. Finally, we could not obtain some unpublished data on the mean duration of ventilation and stay in intensive care.

Our results should be interpreted in light of the heterogeneity of trial results and possible publication bias. More evidence is needed before firm conclusions can be made on the full effect of oral decontamination using antiseptics and, particularly, antibiotics.

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