Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials

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CRD summary
This review concluded that probiotics were associated with lower incidence of ventilator-associated pneumonia than controls in patients who underwent mechanical ventilation. This was a generally well-conducted review and the authors’ conclusions appeared to reflect the evidence. But, interpretation should take into account the small number of studies and participants and the specific type of patients included in the review.

Authors' objectives
To assess the effects of probiotics on the incidence of ventilator-associated pneumonia in patients undergoing mechanical ventilation.

Searching
PubMed (1950 to April 2009), SCOPUS, Current Contents and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant articles in any language. Search terms were reported. Reference lists of retrieved articles were searched manually. Abstracts of conference proceedings and publications that did not provide original data were excluded.

Study selection
Randomised controlled trials (RCTs) that compared the effects of probiotics (with or without prebiotics) versus control (placebo or other, but without probiotics) in adults undergoing mechanical ventilation were eligible for inclusion. The primary outcome of interest was incidence of ventilator-associated pneumonia (as defined in the review). Secondary outcomes of interest were all-cause mortality (intensive care unit (ICU) and in-hospital), length of ICU stay, duration of mechanical ventilation (until patient's death or extubation), colonisation of respiratory tract with *Pseudomonas aeruginosa* and incidence of diarrhoea and/or probiotic-induced bacteraemia/fungaemia.

Included RCTs (published after 2005) were conducted in UK, France, Sweden, Slovenia and Greece. Most studies were carried out in a single centre. RCTs were of general patients, medical-surgical patients and patients with severe multiple trauma/injury who required mechanical ventilation for more than 24 or 48 hours or at least a four-day stay in ICU. Between 6% and 100% were trauma patients. Probiotics included Synbiotic 2000 FORTE, *Lactobacillus casei rhamnosus* and *Lactobacillus plantarum* administered once or twice daily via nasogastric/orogastric tube or applied to the mucosal surface of the oral cavity for 15 or 28 days, or until ICU discharge or death. Some patients received concurrent systemic antimicrobials during ICU stay, administered for treatment of ventilation-associated pneumonia as well as other infections (such as bloodstream and urinary tract infections). The definition of ventilation-associated pneumonia/cultures required for diagnosis was similar among most studies.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Methodological quality of the studies was assessed using a modified Jadad score with criteria on randomisation methods, allocation concealment, double blinding and withdrawals. Scores ranged from 0 to 5.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted continuous outcomes to calculate mean differences and 95% confidence intervals (CIs), and extracted dichotomous outcomes to calculate odds ratios (ORs) and 95% CIs.
**Methods of synthesis**
Fixed-effect and random-effects models were used to pool weighted mean differences (WMDs) and odds ratios, and their 95% CIs.

Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Further analyses were undertaken by removal of RCTs that used different probiotic regimens or used different methods to administer probiotics, RCTs that reported a high incidence of ventilation-associated pneumonia and RCTs that reported the longest ICU stay. Subgroup analyses were undertaken with studies grouped by the microorganisms that causing ventilation-associated pneumonia.

Publication bias was not assessed as the analyses included fewer than 10 studies.

**Results of the review**
Five RCTs were included in the review (n=795 initially enrolled, n=689 analysed). Sample sizes ranged from 50 to 300. Two RCTs scored 5 on the Jadad scale (high quality). One study scored 4. Two RCTs scored 2.

**Incidence of ventilation-associated pneumonia (five RCTs):** Patients who underwent mechanical ventilation and received probiotics reported statistically significantly fewer incidences of ventilation-associated pneumonia compared with controls (OR 0.55, 95% CI 0.31 to 0.98, random-effects model). There was no evidence of statistical heterogeneity according to the fixed-effect model.

Subgroup analyses that included only RCTs with similar probiotic regimens and similar administration techniques did not significantly alter the results. However, after removal of the RCT with high incidence of ventilation-associated pneumonia, the results were no longer statistically significant. Subgroup analyses by underlying microorganism showed no significant differences in incidence of ventilation-associated pneumonia between patients who received probiotics and control.

**Length of ICU stay (three RCTs):** Patients who received probiotics had shorter ICU stays compared with controls when a fixed-effect model was used (WMD -0.99 days, 95% CI -1.37 to -0.61) but not when a random-effects model was used. Eliminating the RCT that reported the longest ICU stay did not significantly alter the results.

There were no statistically significant differences between probiotic and control groups in all-cause mortality during ICU stay (four RCTs), in-hospital stay (two RCTs), duration of mechanical ventilation (three RCTs) or diarrhoea (two RCTs).

Results for other secondary outcomes were reported in the review.

**Authors’ conclusions**
Probiotics were associated with lower incidence of ventilator-associated pneumonia compared with controls.

**CRD commentary**
The review question and supporting inclusion criteria were clearly defined. An adequate search of the literature was conducted with no restriction on language, which reduced potential for language bias. However, abstracts were excluded which meant that potentially relevant data may have been missed. The authors assessed studies for methodological quality using previously published criteria and found the quality of most studies was high. The authors did not state how many authors performed the validity assessment, which meant that reviewer error and bias could not be ruled out. Some information was provided about individual studies, but details of control treatments were missing. Appropriate methods were used to pool data and investigate statistical heterogeneity. The authors acknowledged the paucity of evidence and other limitations with the included studies and evidence synthesis. This was a generally well-conducted review and the authors’ conclusions appeared to reflect the evidence. But, when interpreting the findings the small number of studies and participants and the specific type of patients included in the studies should be borne in mind.

**Implications of the review for practice and research**
The authors did not state any implications for practice.
Research: The authors stated that further research was needed in this area. Future studies should collect an adequate number of blood cultures for each patient to further assess their safety. The authors also suggested that future research may benefit from focusing on assessing the effects of probiotics on ventilation-associated pneumonia in trauma patients.

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