Int J Clin Exp Med 2018;11(10):10269-10277
www.ijcem.com /ISSN:1940-5901/IJCEM0071942

Review Article

Probiotics are effective in decreasing the incidence of ventilator-associated pneumonia in adult patients: a meta-analysis of randomized controlled trials

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Received July 25, 2017; Accepted May 14, 2018; Epub October 15, 2018; Published October 30, 2018

Abstract: Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections found in intensive care units (ICU). Previous studies have found probiotics to be beneficial for a range of diseases. This present study investigated whether they could prevent VAP in critically ill patients. PubMed and Web of Science were searched to identify appropriate randomized controlled trials. The study included a total of 10 studies with 1,403 patients. Heterogeneity was analyzed by Cochran's Q statistic and pooled Mantel-Haenszel relative risks were calculated using either a fixed-effects or random-effects model. Results showed a significant difference between patients given probiotics (25.71%) and the control group (32.70%) in terms of incidence of VAP (odds ratio (OR) 0.69, 95% confidence interval 0.54 to 0.88, P = 0.003). There was also a significant difference (P = 0.0001) between the group given probiotics and the control group in terms of antibiotic usage for VAP (mean deviation -3.00, 95% CI -5.96 to -0.04): antibiotics were given over fewer days in the probiotics group. However, there were no significant differences in terms of incidence of diarrhea (OR = 0.72, 95% CI = 0.49 to 1.09, P = 0.12), ICU mortality (OR 0.95, 95% CI 0.67 to 1.33, P = 0.76), hospital mortality (OR = 0.86, 95% CI = 0.62 to 1.18, P = 0.35), length of ICU stay (MD = -1.74, 95% CI = -6.74 to 3.27, P = 0.50), or duration of mechanical ventilation (MD = -6.21, 95% CI = -18.83 to 6.41, P = 0.34). In this meta-analysis, reduced incidence of VAP in ICU patients given probiotics was found. It seems likely that probiotics provide clinical benefits.

Keywords: Ventilator-associated pneumonia, probiotics, intensive care unit

Introduction

Bacterial translocation, one of the main causes of infection, occurs via three primary routes: overgrowth of bacteria in the small intestines, increased permeability of the intestinal mucosal barrier, and deficiencies in host immune defenses [1]. Probiotics are live non-pathogenic microbes that can limit bacterial translocation through regulating release of pro-inflammatory cytokines, as well as balancing the microenvironment and slowing growth of pathological microorganisms. Previous studies have shown that they are beneficial in cases of necrotizing enterocolitis, diarrhea, post liver transplantation infection, and severe craniocerebral trauma [2-12]. This study, therefore, examined their effects on ventilator-associated pneumonia, which can be caused by bacterial infections.

Ventilator-associated pneumonia (VAP), one of the most common nosocomial infections, occurs when pernicious microbes, that normally present in the nasopharynx, are aspirated into the lungs [13]. It is defined as a pneumonia that develops more than 48 hours after endotracheal intubation. It is common in intensive care units (ICU). Incidence of VAP increases with length of ICU stay [14]. Since probiotics can improve intestinal microbial balance by outcompeting pernicious microbes [13, 15], they may be also beneficial in cases of VAP.

Several previous randomized controlled trials (RCTs) have evaluated the efficacy of probiotics

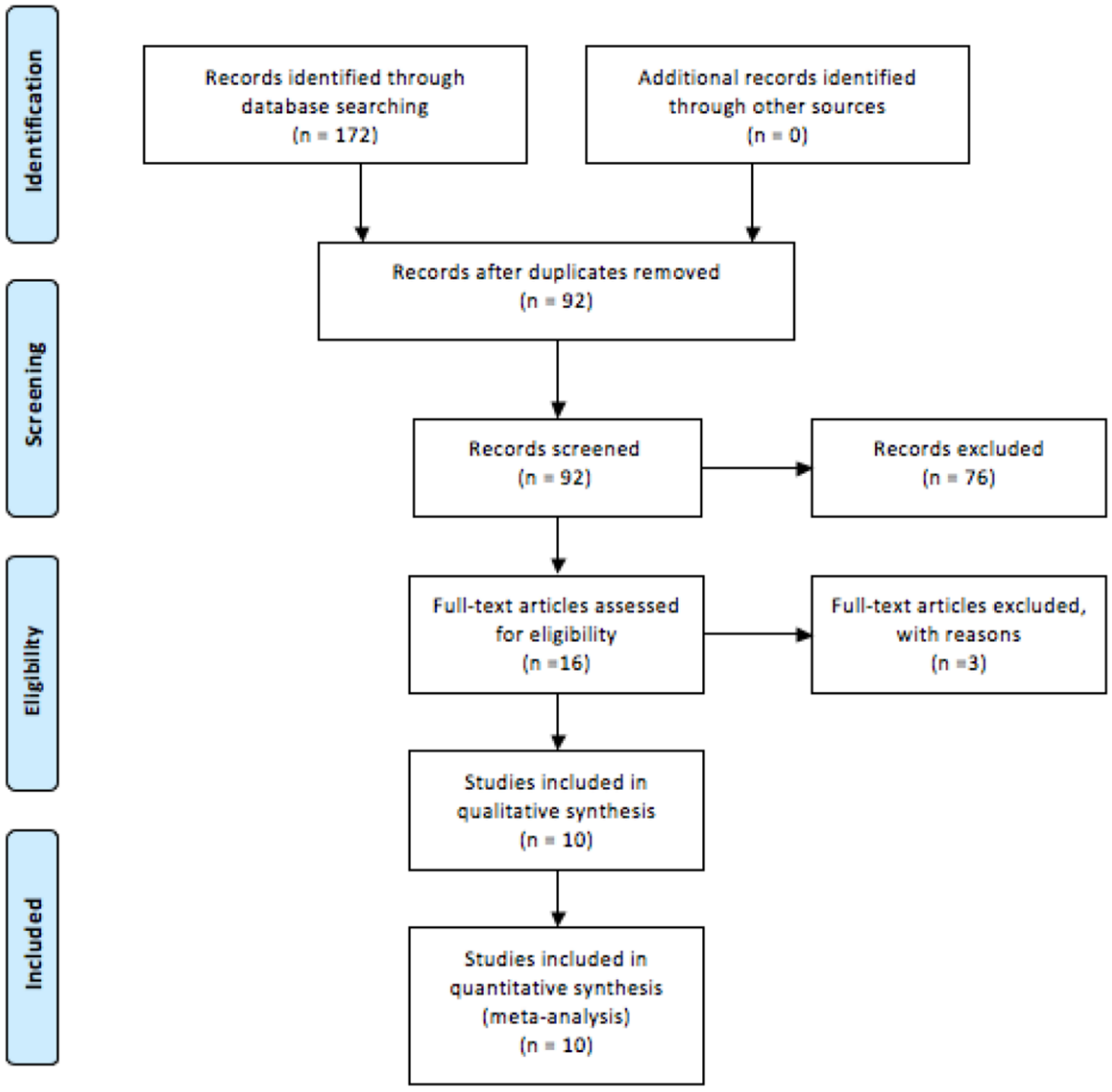

Figure 1. Flow chart of study inclusion.

in preventing VAP [13-20]. Two previous meta-analyses of these RCTs have shown that probiotic therapy can reduce incidence of VAP in ICUs [21, 22]. However, the conclusion of these meta-analyses has been challenged because of selection methodology [23]. However, recent publications with further evidence justify an updated meta-analysis [24, 25]. This could help ICU clinicians treat VAP patients more effectively and appropriately. Therefore, this meta-analysis was conducted to more completely evaluate the efficiency of probiotics in preventing VAP.

Materials and methods

Search strategy

Two reviewers, independently, searched PubMed and Web of Science for human clinical trials regarding probiotics and VAP, with a terminal date of 2017-06. Search terms included "prebiotics", "probiotics", "synbiotics", "lactobacillus", "bifidobacterium", "lactobacilli", "ventilator-associated pneumonia", and "VAP". Reference lists of eligible studies and relevant papers were also manually searched to identify further relevant articles.

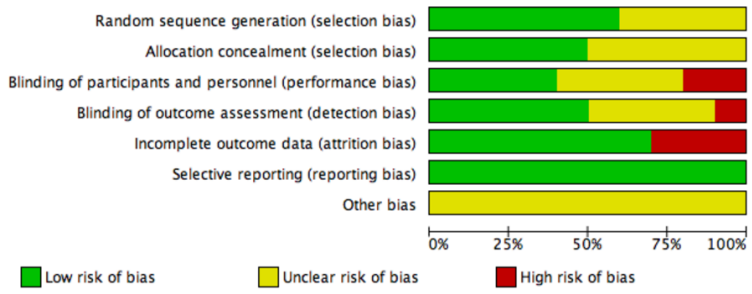

Figure 2. Risk of bias graph: author judgements about each risk-of-bias item presented as percentages across all included studies.

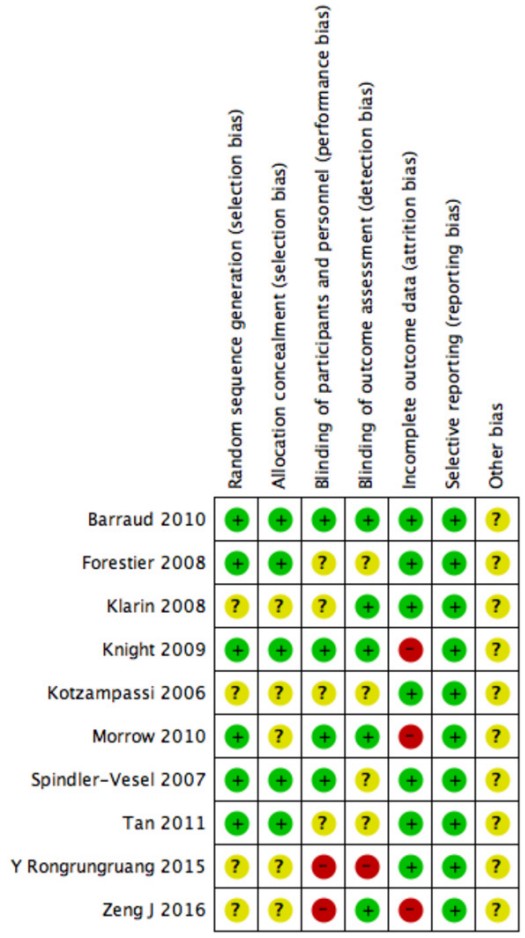

Figure 3. Risk of bias summary: author judgements about each risk-of-bias item for each included study.

Study inclusion

Studies were considered eligible if they met the following inclusion criteria: (1) Randomized controlled clinical trials; (2) Adult participants (≥ 18 years); (3) A comparison of probiotics with placebo or other drugs; and (4) A primary outcome measure of VAP incidence and secondary outcome measures including ICU and hospital mortality. Exclusion criteria were: (1) Retrospective studies or case reports; (2) Participants < 18 years; and (3) No comparator group.

Data extraction

Two investigators, independently, reviewed the identified abstracts and selected articles for full review. Discrepancies were resolved by a third reviewer. For each selected publication, the following baseline and study characteristics were extracted: publication year, country, study design, participant characteristics, and probiotics used. Primary outcome measure was incidence of VAP while secondary outcome measures included ICU mortality, hospital mortality, diarrhea, length of ICU stay, duration of mechanical ventilation, and duration of antibiotic administration. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.

Risk of bias assessment

Risk of bias of trials included in this meta-analysis was assessed according to recommendations of the Cochrane Handbook of Systematic Reviews of Interventions, in the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting) (http://handbook. cochrane. org).

Data synthesis

For dichotomous outcomes, such as incidence of VAP and mortality, summary statistics for each study were calculated as an odds ratio (OR, with 95% confidence interval [CI]). For continuous outcomes, such as duration of mechanical ventilation and ICU length of stay, mean deviation (MD) was used. Data was pooled and expressed as an OR with 95% CI. A fixed-effect model was used if there was no considerable heterogeneity among studies, indicated by I^2

Table 1. Baseline characteristics of all studie

	Study location	Participants	Case number, gender, age		Intervention		Outcome measurements
			Probiotic group	Control group	Probiotic group	Control group	
Kotzampassi. 2009	5 ICUs; University's Hospitals and the Military Hospital, Greece	Trauma patients; tracheal intubation in ICU.	36 52.9 ± 19 28/7	36 55.9 ± 18 25/5	The synbiotic preparation consisted of a combination probiotics; *Pediococcus pentoseceus*, *Leuconostoc mesenteroides*, *L. paracasei* ssp, and *L. plantaru;* for 15 days.	The placebo preparation consisted of identical doses of powdered glucose polymer.	New or persistent consolidation in lung X-ray; purulent tracheobronchial secretion; and a clinical pulmonary infection score of more than 6.
Knight. 2009	1 ICU, 1 center; tertiary care University Hospital; UK	Intubated adult patients for at least 48 h; enteralnutrition.	130 49.5 ± 19.6 81/49	129 50.0 ± 18.5 80/49	At least 2 days of Synbiotic 2000 FORTE®, twice a day; through a nasogastric/orogastric tube.	Crystalline cellulose-based placebo.	New progressive, or persistent, infiltration on chest radiograph plus at least 2 of the following: (1) temperature 38.0°C, (2) WBC count > 12×10^3 μL^{-1} or < 4×10^3 μL^{-1}), (3) purulent secretions.
Klarin. 2008	1 ICU; 1 center, University Hospital, Lund, Sweden	Patients with 18 years of age or older; with an need for 24 h MV.	23 70 (20-87) 13/10	21 70 (43-81) 9/12	Lp299 was applied to the mucosal surface of the oral cavity. A solution containing a total 10^{10} CFUs of Lp299.	Treated according to the department's standard protocol.	A infiltrate on chest radiograph combined with at least 3 criteria; a purulent tracheal aspirate; positive culture of tracheal aspirates occurring after 48 h of MV; rectal temperature higher than 38.0°C or < 35.5°C; WBC > 12 or < 3.
Forestier. 2008	A ICU; 1 center; the hospital of Clermont-Ferand, France	Patients ≥ 18 years with a stay longer than 48 h.	102 60 (18-91) 65/37	106 57 (18-80) 81/25	*L. casei rhamnosus* (10^9 CFU) twice daily.	Placebo (growth medium without bacteria).	At least 1 positive sample; presence of 1 or several new abnormal radio graphical and progressive parenchymatous infiltrates and 1 of the following: purulent sputum, fever, pathogenic bacteria in blood culture.
Spindler-Vesel. 2007	A ICU, one center; Ljubljana, Slovenia	Patients with an ISS of 18 and at least a 4 days ICU stay.	26 48 (29.5-60) None	87 None None	Nutricomp standard and a supplement of a synbiotic consisting of *Pediococcus pentosaceus*, *Lactococcus raffinolactis*, *Lactobacillus paracasei* subsp *paracasei*, *Lactobacillus plantarum*.	3 arms: All contain protein, carbohydrate, fat, et al.	Specimens were collected and nosocomial infections were recorded as recommended.
Zeng. 2016	11 ICUs in nine Chinese teaching hospitals, China	All adult patients (age ≥ 18 years) with an need of MV for 48 h	118 50.2 ± 18.2 73/45	103 54.6 ± 17.9 65/52	Probiotics capsules 0.5 g three times daily plus standard preventive strategies. contained active *Bacillus subtilis* and *Enterococcus faecalis*.	The control group received standard preventive strategies only.	Presence of a new, persistent or progressive infiltrate on chest radiographs that persisted for at least 48 h combined with at least two of the following criteria: (1) temperature of > 38.0°C or < 35.5°C; (2) WBC > $12 \times 10^3/mm^3$ or < $3 \times 10^3/mm^3$ and/or left shift; (3) purulent tracheal aspirates.
Rongrungruang. 2015	A teritary care university hospital in Bangkok, Thailand	Adult patients; were expected to receive MV for at least 72 h.	75 73.09 ± 13.16 32/43	75 68.95 ± 18.45 30/45	Containing 8×10^9 cfu of *Lactobacillus casei* for oral care.	The patients did not receive any additional products.	A infiltrate on a chest radiograph in combination with at least 3 of the following: (1) temperature > 38°C or < 35.5°C, (2) WBC > 10,000 leukocytes/mm^3 or < 3,000 leukocytes/mm^3, (3) purulent tracheal aspirate, and (4) positive semi-quantitative culture of tracheal aspirate samples.
Tan. 2011	A ICU of Hospital of North Sichuan Medical College, Nanchong, China	Closed head injury; Glasgow score between 5 and 8; aged 18-60 years old.	16 40.5 ± 13.0 19/7	19 40.8 ± 12.8 21/5	Golden Bifid (*Bifidobacterium longum*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus)*; administered through a nasogastric tube for 21 days.	Enteral nutrition within 48 h following hospital admission by nasogastric tube.	Radiographic infiltrate plus at least two clinical features - fever > 38.0°C, leucocytosis (WBC> 12×10^9/l), leucopenia (WBC < 4×10^9/l), or purulent tracheobronchial secretions-and positive semiquantitative cultures of tracheobronchial secretions.
Morrow. 2011	A university hospital; provides level 1 trauma services, USA	Adults ≥ 19 years old and require MV with an endotracheal tube for 72 h.	68 52.5 ± 19.3 43/30	70 54.6 ± 16.3 43/30	2×10^9 CFU of *Lactobacillus rhamnosus* GG on a twice-daily basis.	Identical appearing capsules containing the inert plant starch inulin to patients randomized to placebo.	Quantitative cultures of distal airways samples were obtained by non-bronchoscopic bronchoalveolar lavage using a protected catheter. A infiltrate on chest radiographs with 2 of 3 following: fever (> 38.5°C or, < 35.0°C), leukocytosis (WBC < 10,000/mm^3 or < 3000/mm^3) and purulent sputum.
Barraud. 2010	A ICU, 1 center France	All intubated adult patients under MV for at least 2 days.	78 59.1 ± 15.9 33/5	71 61.8 ± 15.5 35/9	5 Ergyphilus® capsules once a day. (*Lactobacillus rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus acidophilus, Bifidobacterium bifidum*); for < 28 days.	Placebo capsules only contained the excipient.	(1) a infiltrate on chest radiograph associated with at least one of the following: purulent tracheal secretions, temperature 38.3°C or higher, and a leukocyte count of 10,000 μL^{-1} or higher; and (2) positive quantitative cultures from bronchoalveolar lavage.

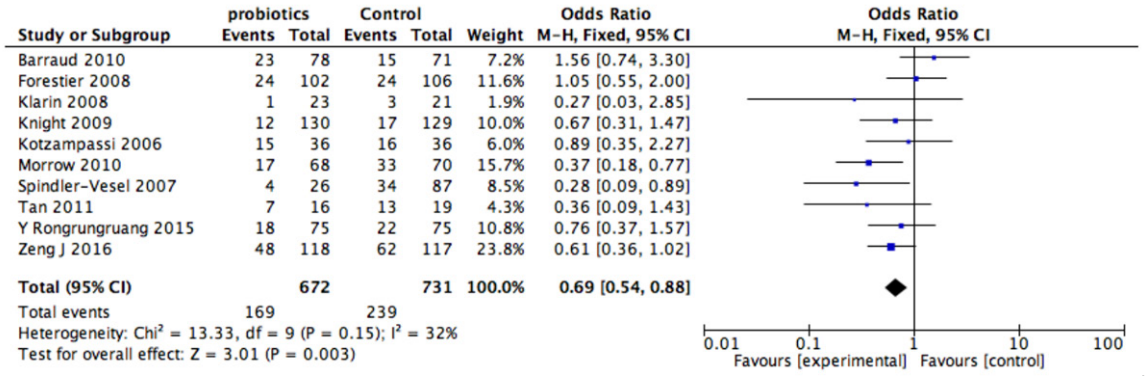

Figure 4. Probiotics versus control: incidence of VAP.

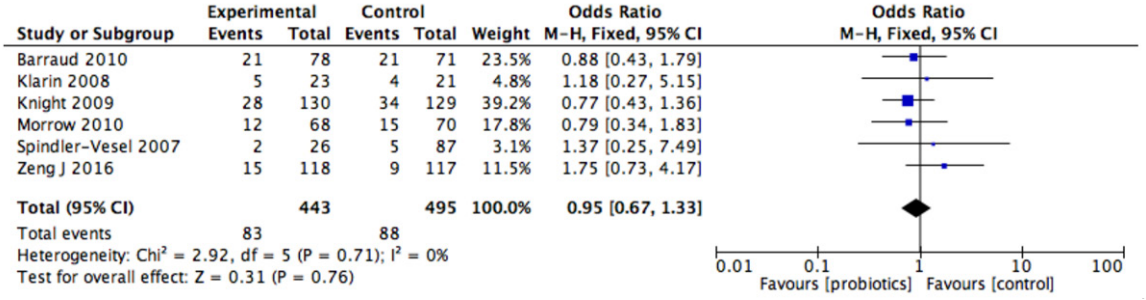

Figure 5. Probiotics versus control: ICU mortality.

value ≤ 50% and Cochran's Q statistic with *P* value > 0.1. Random-effects model was used if I^2 statistic was > 50% and Q statistic had *P* value ≤ 0.1. All statistical analyses were carried out using Review Manager 5.2 (Cochrane Collaboration).

Results

Study characteristics and methodologies

After an initial literature search in the two main electronic databases (PubMed, Web of Science), 101 potentially relevant publications were identified. Of these, 10 trials met the inclusion criteria and were selected for the meta-analysis [13-15, 17-23] (**Figure 1**). All studies were found to have low bias (**Figures 2**, **3**). This present meta-analysis included 1,403 participants (672 given probiotic, 731 controls). The studies were conducted between 2006 and 2016 in China [20, 25], France [15, 16], Greece [17], Slovenia [19], Sweden [14], the UK [13], the USA [18] and Thailand [24]. **Table 1** presents the basic characteristics of included trials and demographic data of participants. Two trials were multicenter studies enrolling participants of various ethnicities.

Incidence of VAP

Incidence of VAP was significantly less in the probiotics group (25.71%) compared to the control group (32.70%), based on a fixed-effects model (OR = 0.69, 95% CI = 0.54 to 0.88, P = 0.003). Heterogeneity testing showed that I^2 = 32%, indicating low heterogeneity across included studies (**Figure 4**).

ICU mortality

In a total of six pooled studies, including 938 patients, there was no significant difference between patients given probiotics (18.74%) and the control group (17.78%) in terms of ICU mortality, based on a fixed-effects model (OR = 0.95, 95% CI = 0.67 to 1.33, P = 0.76). Heterogeneity testing showed that I^2 = 0%, indicating low heterogeneity (**Figure 5**).

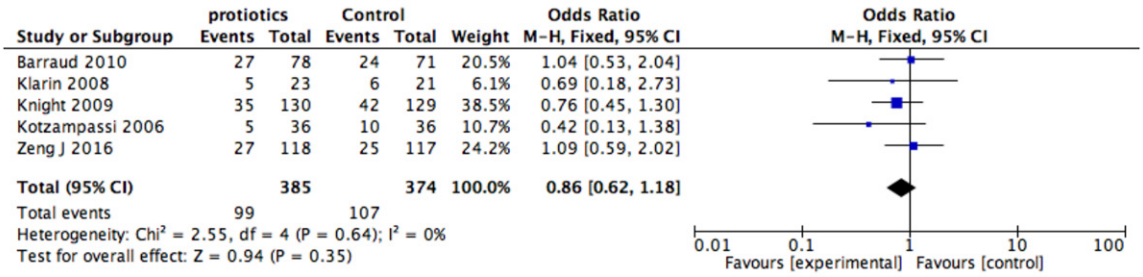

Figure 6. Probiotics versus control: hospital mortality.

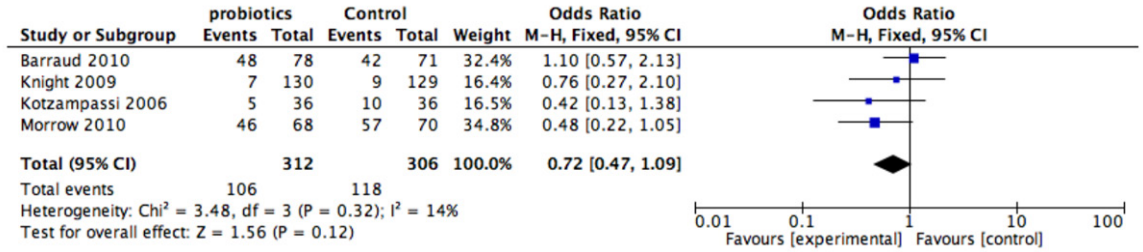

Figure 7. Probiotics versus control: incidence of diarrhea.

Hospital mortality

Analysis of five studies, including 759 patients, showed no significant difference between patients given probiotics (25.71%) and the control group (28.61%) in terms of hospital mortality, based on a fixed-effects model (OR = 0.86, 95% CI = 0.62 to 1.18, P = 0.35). Heterogeneity testing showed that I^2 = 0%, indicating low heterogeneity (**Figure 6**).

Diarrhea

Assessment of four studies, including 618 patients, showed no significant difference between the group given probiotics (33.97%) and the control group (38.52%) in terms of incidence of diarrhea, based on a fixed-effects model (OR = 0.72, 95% CI = 0.49 to 1.09, P = 0.12). Heterogeneity testing found that X^2 = 3.48 (P = 0.32) and I^2 = 14%, indicating low heterogeneity (**Figure 7**).

Length of ICU stay

A total of four pooled studies, with 432 patients, showed no significant difference between the group given probiotics and control group in terms of length of ICU stay, based on a random-effects model (MD = -1.74, 95% CI = -6.74 to 3.27, P = 0.50, **Figure 8**). Heterogeneity testing showed that I^2 = 79%. Subgroup analysis was performed by removing one study (Kotzampassi 2009) because of high risk of bias. Subgroup analysis showed similar results to overall analysis (MD = 1.25, 95% CI = -1.28 to 3.79).

Duration of mechanical ventilation (days)

Two trials were analyzed, including 215 patients, in terms of duration of mechanical ventilation. There was no significant difference between the group given probiotics and the control group, based on a random-effects model (MD = -6.21, 95% CI = -18.83 to 6.41, P = 0.34). The I^2 value of 93% (**Figure 9**) indicated a considerable level of heterogeneity.

Duration of Antibiotic use for VAP (days)

A pool of two trials, including 381 patients, showed significantly greater use (P = 0.0001) of antibiotics for VAP in patients given probiotics than the control group, based on a fixed-effects model (MD = -3.00, 95% CI = -5.96 to -0.04, P = 0.04). The I^2 value of 31% indicated a low level of heterogeneity (**Figure 10**).

Discussion

Ventilator-assisted pneumonia, caused by pathological microbes colonized at the naso-

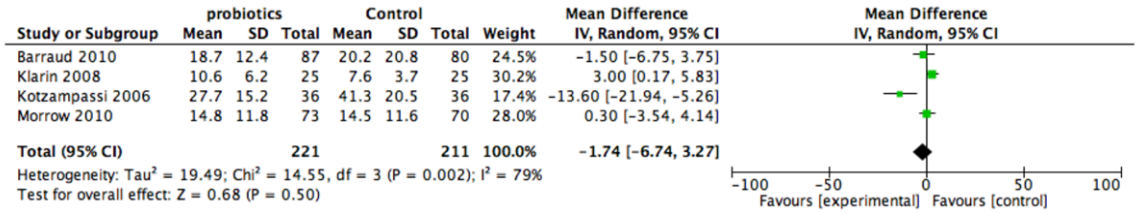

Figure 8. Probiotics versus control: length of ICU stay (days).

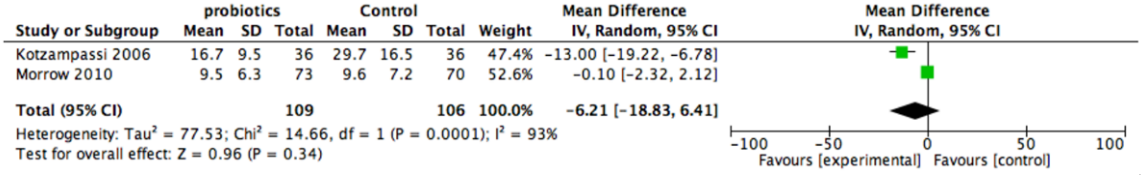

Figure 9. Probiotics versus control: duration of mechanical ventilation (days).

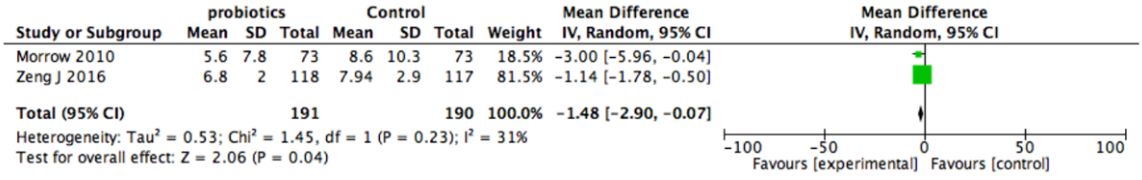

Figure 10. Experimental versus control: days of antibiotics prescribed for VAP.

pharynx, is a dangerous complication in ICUs, with high mortality and poor prognosis. The usual method of treatment is use of a broad-spectrum antibiotic.

However, probiotics are sometimes used for prophylaxis due to their beneficial effects. These include stimulation of gut immunity, outcompeting pathogenic bacteria for nutrients, production of bacitracin and organic acids, competitive inhibition of bacterial attachment sites, and increased trans-epithelial resistance. These help to limit the translocation of intestinal microbes and benefit the immune system through repairing intestinal mucosa and regulating release of cytokines. Guidelines on probiotics, produced by the World Gastroenterology Organization, states that gut microbiota may affect several non-gastrointestinal conditions. Numerous studies have shown that probiotics can reduce bacterial vaginosis, prevent atopic dermatitis in infants, reduce oral pathogens and dental caries, and reduce incidence and duration of common upper respiratory tract infections [26]. In addition, several studies have investigated the prophylactic use of probiotics in protecting against VAP, although results have not been conclusive.

This present meta-analysis included a total of 1,403 patients across 10 RCTs. Overall, heterogeneity of the studies was low. Probiotics seemed to be effective in reducing incidence of VAP and there was also a significant effect in terms of duration of antibiotics prescribed for VAP. A further reason could be that probiotics are given to replace beneficial bacteria killed by antibiotics, thereby balancing the microorganism environment in the body. Therefore, probiotic use for VAP prevention should be recommended in clinical practice.

However, there was no evidence that probiotics could decrease ICU or hospital mortality or incidence of diarrhea. This could be due to patients in ICU often having multiple critical illnesses that do not benefit from probiotics, such as heart failure, respiratory failure, and severe pneumonia. Across all three analyses, heterogeneity was low, indicating that results were valid. There were also no significant effects of probiotics in terms of length of ICU stay or dura-

tion of ventilator with considerable levels of heterogeneity.

New guidelines produced by the Infectious Diseases Society of America [27] have provided a new definition for Hospital Associated Pneumonia, broadening the definition of VAP to include patients contracting pneumonia after a hospital stay > 48 hours with ventilator support. This means that more patients could be diagnosed with VAP and enrolled in further studies, providing more evidence.

Reasons for why probiotics prevent incidence of VAP are complicated, but it is likely related to how they modulate the intestinal microenvironment, limiting the growth of pathological bacteria.

Disclosure of conflict of interest

None.

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