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

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**Background:** Previous reviews showed no benefit for the administration of probiotics in critically ill patients, but they did not focus on ventilator-associated pneumonia.

**Design:** Meta-analysis of randomized controlled trials comparing probiotics and control in patients undergoing mechanical ventilation and reporting on incidence of ventilator-associated pneumonia.

**Methods:** PubMed, Scopus, Current Contents, Cochrane Central Register of Controlled Trials, and reference lists were searched. Weighted mean differences, pooled odds ratios, and 95% confidence intervals were calculated, implementing both the Mantel-Haenszel fixed effect and the DerSimonian-Laird random effects model.

**Results:** Five randomized controlled trials were included. Administration of probiotics, compared with control, was beneficial in terms of incidence of ventilator-associated pneumonia (689 patients; fixed effect model: odds ratio, .61; 95% confidence interval, .41–.91; random effects model: odds ratio, .55, 95% confidence interval, .31–.96), length of intensive care unit stay (fixed effect model: weighted mean difference, −0.99 days; 95% confidence interval, −1.37–−.61), and colonization of the respiratory tract with *Pseudomonas aeruginosa* (odds ratio, .35; 95% confidence interval, .13–.93). However, no difference was revealed between comparators regarding intensive care unit mortality (odds ratio, .75; 95% confidence interval, .47–1.21), in-hospital mortality (odds ratio, .75; 95% confidence interval, .46–1.24), duration of mechanical ventilation (weighted mean difference, −0.01 days; 95% confidence interval, −.31–.29), and diarrhea (odds ratio, .61; 95% confidence interval, .28–1.34).

**Conclusion:** Administration of probiotics is associated with lower incidence of ventilator-associated pneumonia than control. Given the increasing antimicrobial resistance, this promising strategy deserves consideration in future studies, which should have active surveillance for probiotic-induced diseases. (Crit Care Med 2010; 38:000–000)

**KEY WORDS:** nosocomial pneumonia; respiratory tract infection; symbiotic; probiotic; prevention; adjunctive.

Probiotics are commercially available microorganisms, which, when administered in adequate amounts, either as individual strains or in various combinations, have health benefits for the host (1). Probiotics are often administered with nondigestible food ingredients that facilitate bacterial growth and/or activity (prebiotics); products containing both probiotics and prebiotics are called synbiotics (1). Administering probiotics has been advocated as a means to prevent various infections, including ventilator-associated pneumonia (VAP), in the setting of ICU (2, 3). The pathogenetic rationale behind the putative action of probiotics against VAP could be their competition with pathogens and, thus, the reduction of the density of the latter in the oropharynx and stomach of patients undergoing mechanical ventilation (MV) (2). More recently, it has been reported that the effectiveness of probiotics against infection may be better explained by their immunomodulatory properties (4, 5).

Although rare reports of probiotic-induced diseases retain the skepticism regarding the safety of probiotics, several well-known advantages, such as low cost, ease of administration, and minimal toxicity, make them a promising strategy to prevent respiratory tract infections, for example, community-acquired ones (6), especially in our era of increasing antimicrobial resistance, in which researchers and clinicians redirect their interest to adjunctive, nonantimicrobial options to fight infections (7).

During the past months, a number of well-performed randomized controlled trials (RCTs) directly exploring the role of probiotics in preventing VAP were published. This is a fact that substantially widened the relevant evidence base. We endeavored to appraise and synthesize this growing body of evidence regarding the impact of administration of probiotics on the incidence of VAP by performing a meta-analysis of RCTs.

**MATERIALS AND METHODS**

**Data Sources**

We conducted this meta-analysis by following the guidelines from the quality of reporting of meta-analyses conference (8). To trace potentially relevant RCTs, we systematically searched PubMed (publications archived from January 1950–April 2009), Scopus, Current Contents, and the Cochrane Central Register of Controlled Trials by using the following search phrase: ["pneumonia" OR "critically ill"] AND ["probiotics" OR "prebiotics" OR "synbiotics" OR "lactobacillus" OR "bifidobacterium"] and also reviewed the references of the initially retrieved trials.

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Study Selection

Two reviewers (IIS and TKN) independently performed literature searches and evaluated the eligibility of the identified publications. We considered for inclusion in this meta-analysis RCTs that compared administration of probiotics vs. control (placebo or other) in adult patients undergoing MV and reported on incidence of VAP. Probiotics could be administered either alone or in combination with prebiotics. We set no limitations regarding the time or language of publications. We omitted abstracts of conference proceedings, publications not providing original data, experimental investigations, studies that enrolled children, and those reporting on outcomes other than incidence of pneumonia. In addition, we excluded articles that referred to pneumonia in critically ill patients in general without specific mention in VAP. Finally, we did not consider RCTs that used probiotics in both study arms.

Data Extraction

Two reviewers (IIS and TKN) independently extracted the following data from each study: first author, year of publication, country where trial was executed, study design, type of ICU and study population, number of initially enrolled individuals, number of evaluated participants, proportion of the evaluated patients who were trauma patients, severity of illness on ICU admission, concurrent administration of systemic antimicrobial agents, definition of VAP used, and cultures required for confirmation of VAP diagnosis in each of the included trials. Information dealing with the probiotic regimen used (with details regarding the kind and the amount of contained strain), dosage, mode of administration, and duration of probiotic treatment was also gathered. Data on the incidence of VAP, mortality, length of ICU stay, duration of MV, colonization of respiratory tract, diarrhea, and toxicity were also extracted from the selected articles. Regarding the evaluation of the methodologic quality of included RCTs, we used a modified Jadad score, which considers the following components: randomization, generation of random numbers, details of double-blinding procedure, information on withdrawals, and concealment of allocation; the maximum and minimum scores for a study are 5 and 0, respectively (9).

Analyzed Outcomes and Definitions

Outcomes. Incidence of VAP was the main outcome of the present meta-analysis. All-cause mortality (both ICU and in-hospital mortality), length of ICU stay, duration of MV (until patient’s death or extubation), colonization of respiratory tract with *Pseudomonas aeruginosa*, and the number of patients experiencing diarrhea and/or probiotic-induced bacteremia/fungemia served as secondary outcomes.

VAP. Clinical (fever or hypothermia, purulent tracheal secretions), laboratory (leucocytosis or leucopenia), and imaging (new and persistent infiltrate on chest radiograph) findings were used to define pneumonia, which was considered as ventilator-associated when occurred in patients receiving MV for at least 48 hrs.

Data Analysis and Statistical Methods

Review Manager (RevMan version 4.2.8; Copenhagen, Nordic Cochrane Center, Cochrane Collaboration, 2003) was used to perform statistical analyses. The presence of heterogeneity among trials was assessed by using the chi-square test ($p < .10$) denoted statistical significance in the analysis of heterogeneity), whereas the extent of inconsistency was assessed using $I^2$ statistic, as previously described (10, 11). Given that the number of included trials was <10, detection of publication bias was considered meaningless (12). Continuous variables were analyzed using weighted mean differences (WMDs) and 95% confidence intervals (CIs) (13). Pooled odds ratios (ORs) and 95% CIs for categorical variables were calculated by implementing both the Mantel-Haenszel fixed effect (14) and the DerSimonian-Laird random effects model (15).

RESULTS

Selected Randomized Controlled Trials

In Figure 1 we present a flow diagram showing the steps we followed to select the appropriate trials for our meta-analysis. Of the 115 articles that were identified through the initial search in PubMed and reference lists, the majority were excluded for the reasons depicted in Figure 1. Three RCTs, albeit enrolling critically ill patients, were omitted because they: involved children or not designed as randomized controlled trials (n=1) investigated the effect of administration of probiotics on outcomes other than incidence of pneumonia, i.e. incidence of diarrhea (n=0) or pneumonia (n=2) or community-acquired pneumonia (n=1) or mortality (n=3).

Additional eligible RCTs retrieved through searches of:
- Cochrane Central Register of Controlled Trials (n=0)
- Scopus (n=0)
- Current Contents (n=0)

Articles excluded because they were:
- Reviews (n=11) or meta-analyses (n=3) or case reports (n=15) or commentaries (n=6) or guidelines (n=1)
- Animal studies (n=8)
- Laboratory investigations (n=8)

Studies retrieved for final evaluation (n=30)

RCTs enrolling critically ill patients and retrieved for further evaluation (n=8)

Articles that did not meet our inclusion criteria because they:
- Involved children (n=18)
- Were not designed as randomized controlled trials (n=1)
- Investigated the effect of administration of probiotics on outcomes other than incidence of pneumonia, i.e. incidence of diarrhea (n=6) or pneumonia (n=2) or community-acquired pneumonia (n=1) or mortality (n=3)

Additional eligible RCTs retrieved through searches of:
- Cochrane Central Register of Controlled Trials (n=0)
- Scopus (n=0)
- Current Contents (n=0)

RCTs evaluating the impact of administration of probiotics on the incidence of ventilator-associated pneumonia that were finally included in the meta-analysis (n=5)

![Flow diagram](image-url)
Table 1. Characteristics of the Selected Studies

In Table 1 we summarize the characteristics of the five RCTs (19–23) that were included in the current analysis. Their mean sample size was 159 individuals (range, 50–300). All studies (19–23) were published after 2005. The majority of them were double-blind (19, 20, 23), single-center (19–22) trials, with a Jadad score of more than three (19, 20, 23). The proportion of patients undergoing MV who were trauma patients was 100% in two (22, 23), 20% to 25% in two (19, 20), and <10% in the remaining trial (21). Data on severity of illness on ICU admission of the enrolled patients were also available (Table 1).

In the majority of the included RCTs (19, 21–23), qualitative cultures of tracheal aspirates were considered adequate to microbiologically confirm diagnosis of VAP; however, in the remaining trial (20), quantitative cultures (of tracheal aspirates or specimens obtained from bronchoalveolar lavage or protected brush) were required for this purpose.

Study Regimens

In Table 1 we show in detail the probiotic preparations administered as well as dosage, mode, and duration of their administration. Three (19, 22, 23) of the five (19–23) included RCTs used the same regimen, ie, Synbiotic 2000 FORTE (Medipharma, Kågeröd, Sweden, and Des Moines, IA). This synbiotic contains lactic acid bacteria (probiotics: *Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *Lactobacillus paracasei* subspecies *paracasei*, and *Lactobacillus plantarum*) combined with fiber (prebiotics: betaglucan, inulin, pectin, and resistant starch). In the remaining two trials (20, 21), a single-agent probiotic regimen (instead of combination therapy) was administered, namely *Lactobacillus casei rhamnosus* (20) and *Lactobacillus plantarum* 299 (21). In the majority of eligible trials, probiotics were administered twice daily (19–21) via nasogastric/orogastric tube (19, 20, 22, 23) until patient’s discharge from the ICU or death (20–22).

Information on the concurrent administration of systemic antimicrobials in each of the compared groups (ie, probiotics vs. control) was provided by three RCT (19, 20, 23) (Table 1). Most (>90%) of the enrolled patients received concurrent systemic antibiotics at some point during their ICU stay; no difference was noted between the compared groups regarding this characteristic (Table 1). In three (19–21) of the five (19–23) eligible RCTs, a proportion (up to 93%) of enrolled patients received systemic antibiotics at study entry, whereas the remaining two RCTs (22, 23) did not provide relevant data. Antimicrobial agents were administered not only for the treatment of VAP, but also for other infections, such as bloodstream and urinary tract infections.

Incidence of Ventilator-Associated Pneumonia

In Table 2 we depict the outcomes studied in the present meta-analysis. All RCTs (19–23) included in our analysis provided data on the incidence of VAP. No heterogeneity was revealed among the identified comparisons (p = .16; I² = 39%). Incidence of VAP was significantly lower in patients undergoing MV treated with probiotics compared to control (689 patients; fixed effect model: OR, .61; 95% CI, .41–.91; random effects model: OR, .55; 95% CI, .31–.98). The OR for VAP incidence in the individual RCT, as well as the pooled ORs, are shown in Figure 2.

Subgroup Analyses. This finding (ie, lower incidence of VAP in probiotic recipients than in comparators) was retained in the subgroup analysis that we performed after the exclusion of the one RCT (21), in which probiotic regimen was applied to the oral cavity instead of administered via nasogastric/orogastric tube (645 patients; fixed effect model: OR, .62; 95% CI, .41–.94; random effects model: OR, .56; 95% CI, .30–1.06). This was also the case for the subgroup analysis of the three RCTs (19, 22, 23) that used the same probiotic regimen, namely Synbiotic 2000 FORTE (437 patients; fixed effect model: OR, .44; 95% CI, .25–.75; random effects model: OR, .44; 95% CI, .24–.79). As well as for the subgroup analysis after the exclusion of the RCT (23) that reported a high incidence of VAP (624 patients; fixed effect model: OR, .68; 95% CI, .44–1.05; random effects model: OR, .64; 95% CI, .35–1.17); however, the latter finding did not reach statistical significance.

As pertains to the microorganisms that were responsible for causing VAP, two (19, 20) of the five eligible RCTs (19–23) gave specific data. In detail, the culprit pathogens were Enterobacteriaceae (19, 20), *Pseudomonas aeruginosa* (19, 20), *Staphylococcus aureus* (19, 20), *Haemophilus influenzae* (19), *Acinetobacter baumannii* (19), and *Stenotrophomonas maltophilia* (19). No statistically significant differences were revealed between patients receiving probiotics and control on the incidence of VAP caused by Enterobacteriaceae (77 patients; fixed effect model: OR, 1.87; 95% CI, .71–4.93; random effects model: OR, 1.87; 95% CI, .71–4.94), *Pseudomonas aeruginosa* (77 patients; fixed effect model: OR, .31; 95% CI, .08–1.19; random effects model: OR, .31; 95% CI, .08–1.18), or *Staphylococcus aureus* (77 patients; fixed effect model: OR, 1.05; 95% CI, .36–3.02; random effects model: OR, 1.06; 95% CI, .36–3.11).

All-Cause Mortality

Data on all-cause mortality during ICU stay were from four (19, 21–23) RCTs included in the analysis. Heterogeneity was not found among the comparisons (p = .58; I² = 0%). There was no difference between patients receiving probiotics and control with regard to all-cause ICU mortality (481 patients; fixed effect model: OR, .75; 95% CI, .47–.121; random effects model: OR, .76; 95% CI, .47–.121) (Fig. 3).

However, two (19, 21) of the five selected RCTs (19–23) provided information regarding all-cause mortality during the whole hospital stay. Again, heterogeneity was not detected (p = .90; I² = 0%). There was no difference between patients receiving probiotics and control regarding all-cause in-hospital mortality (303 patients; fixed effect model: OR, .75; 95% CI, .46–1.24; random effects model: OR, .75; 95% CI, .46–1.24).

Length of Intensive Care Unit Stay

Three (19, 21, 23) of the five (19–23) RCTs included in the meta-analysis reported on the length of ICU stay. Patients treated with probiotics, as opposed to control, stayed fewer days in the ICU (368 patients; fixed effect model: WMD: –.99 days of ICU stay; 95% CI, –1.37 to –.61); however, this difference was not statistically significant when a random effects model was implemented (WMD: –1.93 days of ICU stay; 95% CI, –5.82 to 1.95). This was also the case for the subgroup analysis we performed after the exclusion of the trial (23) that reported the longest ICU stay among the trials included in our meta-analysis (303 patients; fixed effect model: WMD: –.97 days of ICU stay; 95% CI, –1.35 to –.59; random effects model: WMD: –.49 days of ICU stay; 95% CI, –2.25 to 1.27).
### Table 1. Main characteristics of the randomized controlled trials included in the meta-analysis: Comparison of probiotics vs. control

<table>
<thead>
<tr>
<th>First Author (ref)</th>
<th>Year of Publication/Country</th>
<th>Study Design/Study Quality Score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Type of ICU/Study Population</th>
<th>Probiotic Regimen Used; Probiotic Strain(s) Contained</th>
<th>Dosage; Mode of Administration; Duration of Probiotic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knight (19)</td>
<td>2009/United Kingdom</td>
<td>DB, SC, RCT/5</td>
<td>General/patients (&gt;16 yrs) requiring MV &gt;2 days</td>
<td>Symbiotic 2000 FORTE; <em>Pediococcus pentosaceus</em>, <em>Leuconostoc mesenteroides</em>, <em>Lactobacillus paracasei</em> subspecies <em>paracasei</em>, and <em>Lactobacillus Plantarum</em>, 10&lt;sup&gt;10&lt;/sup&gt; CFU <em>Pediococcus pentosaceus</em>, <em>Leuconostoc mesenteroides</em>, <em>Lactobacillus paracasei</em> subspecies <em>paracasei</em>, and <em>Lactobacillus Plantarum</em></td>
<td>Twice daily; via nasogastric/orogastric tube; until 28 days after ICU admission or ICU discharge or death</td>
</tr>
<tr>
<td>Forestier (20)</td>
<td>2008/France</td>
<td>DB, SC RCT/5</td>
<td>Medical-surgical/patients (&gt;18 yrs) requiring MV &gt;48 hrs</td>
<td>Lactobacillus <em>casei rhamnosus</em>, 10&lt;sup&gt;9&lt;/sup&gt; CFU</td>
<td>Twice daily; via nasogastric/orogastric tube; until ICU discharge or death</td>
</tr>
<tr>
<td>Klarin (21)</td>
<td>2008/Sweden</td>
<td>Open-label, SC, RCT/2</td>
<td>General/patients (&gt;18 yrs) requiring MV &gt;24 hrs</td>
<td><em>Lactobacillus plantarum</em> 299, 10&lt;sup&gt;10&lt;/sup&gt; CFU</td>
<td>Twice daily; applied to the mucosal surface of the oral cavity; until ICU discharge or death</td>
</tr>
<tr>
<td>Spindler-Vesel (22)</td>
<td>2007/Slovenia</td>
<td>SC RCT/2</td>
<td>Surgical/multiple injured patients requiring MV, with an injury severity score of &gt;18 and at least a 4-day ICU stay</td>
<td>Symbiotic 2000 FORTE; <em>Pediococcus pentosaceus</em>, <em>Lactococcus raffinolactis</em>, <em>Lactobacillus paracasei</em> subspecies <em>paracasei</em>, and <em>Lactobacillus Plantarum</em>, 10&lt;sup&gt;10&lt;/sup&gt; CFU</td>
<td>Once daily; via nasogastric/orogastric tube; until ICU discharge or death</td>
</tr>
<tr>
<td>Kotzampassi (23)</td>
<td>2006/Greece</td>
<td>DB, MC RCT/4</td>
<td>Surgical/severe multiple trauma patients (&gt;18 yrs) requiring MV</td>
<td>Symbiotic 2000 FORTE; <em>Pediococcus pentosaceus</em>, <em>Leuconostoc mesenteroides</em>, <em>Lactobacillus paracasei</em> subspecies <em>paracasei</em>, and <em>Lactobacillus Plantarum</em>, 10&lt;sup&gt;10&lt;/sup&gt; CFU</td>
<td>Once daily; via nasogastric/orogastric tube; for 15 days or until ICU discharge or death</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; VAP, ventilator-associated pneumonia; MV, mechanical ventilation; DB, double-blind; SC, single-center; MC, multicenter; RCT, randomized controlled trial; CFU, colony-forming units; PSB, protected specimen brush; BAL, bronchoalveolar lavage.

<sup>a</sup>By using a modified Jadad score; <sup>b</sup>Mean ± SD of the parameter measured rather than median (range) was reported in these randomized controlled trials.
<table>
<thead>
<tr>
<th>Concurrent Administration of Systemic Antimicrobials During ICU Stay</th>
<th>N of Initially Enrolled Patients</th>
<th>N of Evaluated Patients; Proportion of Evaluated Patients Who Are Trauma Patients, %</th>
<th>Severity of Illness on ICU Admission, Median (Range)</th>
<th>Definition of VAP Used/Cultures Required for VAP Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>120/130 (92) vs. 117/129 (91)</td>
<td>300</td>
<td>130 vs. 129; 22%</td>
<td>APACHE II: 17 (12–23) vs. 17 (12–22)</td>
<td>New progressive or persistent (&gt;24 hrs) infiltration on chest radiograph plus at least two of the following: (1) temperature &gt;38°C; (2) leucocytosis (&gt;12,000 μL⁻¹) or leucopenia (&lt;4000 μL⁻¹); (3) purulent tracheal aspirates/qualitative tracheal aspirates</td>
</tr>
<tr>
<td>101/102 (99) vs. 105/106 (99)</td>
<td>236</td>
<td>102 vs. 106; 24%</td>
<td>SAPS II: 45 ± 16 vs. 44 ± 15b</td>
<td>New progressive infiltration(s) on chest radiograph plus at least one of the following: (1) temperature &gt;38.5°C; (2) pathogenic bacteria in blood culture without other infection source; (3) purulent sputum; (4) BAL with &gt;5% cells with intracellular bacteria/quantitative tracheal aspirates or PSB or BAL</td>
</tr>
<tr>
<td>NA</td>
<td>50</td>
<td>23 vs. 21; 6%</td>
<td>APACHE II: 22 (11–39) vs. 27 (9–37)</td>
<td>New progressive or persistent (&gt;24 hrs) infiltration on chest radiograph plus at least three of the following: (1) temperature &gt;38.5°C or &lt;35.5°C; (2) leucocytosis (&gt;12,000 μL⁻¹) or leucopenia (&lt;3000 μL⁻¹); (3) purulent tracheal aspirates, 4) positive culture of tracheal aspirates occurring after 48 hrs of MV/qualitative tracheal aspirates</td>
</tr>
<tr>
<td>NA</td>
<td>132</td>
<td>26 vs. 87; 100%</td>
<td>APACHE II: 14 (12–19) vs. NA</td>
<td>New progressive or persistent infiltration on chest radiograph plus at least two of the following: (1) temperature &gt;38°C; (2) leucocytosis (&gt;10,000 μL⁻¹); (3) purulent tracheal aspirates/qualitative tracheal aspirates</td>
</tr>
<tr>
<td>35/35 (100) vs. 30/30 (100)</td>
<td>77</td>
<td>35 vs. 30; 100%</td>
<td>APACHE II: 19 ± 3 vs. 19 ± 2b</td>
<td>New or progressive infiltration on chest radiograph plus: (1) temperature &gt;38.5°C; (2) leucocytosis (&gt;12,000 μL⁻¹) or leucopenia (&lt;4000 μL⁻¹); (3) purulent tracheal aspirates/qualitative tracheal aspirates</td>
</tr>
</tbody>
</table>
Duration of Mechanical Ventilation

The majority (19, 21, 23) of the eligible RCT provided data on the duration of MV. There was no difference between the compared groups regarding this outcome (368 patients; fixed effect model: WMD: 0.01 days of MV; 95% CI, .31 to .29; random effects model: WMD: 2.24 days of MV; 95% CI, 6.65 to 2.16).

Colonization of the Respiratory Tract With Pseudomonas aeruginosa

Two (20, 21) RCTs included in the meta-analysis gave information regarding the colonization of the respiratory tract with Pseudomonas aeruginosa. No heterogeneity was noted (p = .82; I² = 0%). Fewer patients were colonized with Pseudomonas aeruginosa in the group receiving probiotics compared to the control group (252 patients; fixed effect model: OR, .35; 95% CI, .13–.93; random effects model: OR, .35; 95% CI, .13–.93).

Diarrhea

With respect to the number of patients who experienced diarrhea, two (19, 23) out of the five (19–23) eligible reports provided relevant data. Heterogeneity was not found (p = .19; I² = 42%). Compared groups (i.e., probiotics and control) did not differ on the number of patients who had diarrhea (324 patients; fixed effect model: OR, .61; 95% CI, .28–1.34; random effects model: OR, .60; 95% CI, 21–1.73).

Probiotic-Induced Disease

No episodes of bacteremia attributable to the probiotic regimen administered were encountered in the three RCTs (19, 20, 22) that provided relevant information.

DISCUSSION

By synthesizing data derived from 689 patients undergoing MV, the present...
meta-analysis revealed that administration of probiotics, as opposed to control, seems to be associated with lower incidence of VAP. The fact that this benefit retained in the various subgroup analyses that we executed presumably adds robustness to our main finding. In addition, probiotics are linked to shorter length of ICU stay and lower colonization of respiratory tract with Pseudomonas aeruginosa, but not to lower all-cause mortality or duration of MV than control.

The main finding of our meta-analysis seems to contradict previous reviews on the topic, which disputed the usefulness of probiotics in critically ill patients. In detail, in a meta-analysis by Watkinson et al (24), it was noted that “the use of pre-, pro-, or synbiotics in adult critically ill patients confers no statistically significant benefit in length of ICU stay, hospital mortality, and the incidence of nosocomial infection.” Similarly, in their review on the role of probiotics against nosocomial infections, in which no meta-analysis was performed, Isacow et al (25) concluded that “there is no current clinical evidence to support the use of probiotics to reduce hospital-acquired pneumonia.” However, both contributions (24, 25) were in fact inconclusive, as their authors clearly emphasized, because of the limited (at the time of their publication) available evidence. Besides, none of them focused on VAP (24, 25). In contrast, our meta-analysis incorporated RCTs that were recently published (i.e., after the publication of these reviews) (24, 25) and focused on the preventive role of probiotics against VAP.

Our main finding (i.e., protective effect of probiotics against VAP) is also supported by another relevant double-blind RCT, which is currently presented only in an abstract form (26). Morrow et al (26), by enrolling 40 adults undergoing MV, noted that incidence of clinically diagnosed VAP was lower, albeit not statistically significant, in patients receiving a probiotic formulation (namely Lactobacillus GG) compared to placebo-recipients (probiotic vs. placebo: 5/19 (26%) vs. 10/21 (45%); \( p = .21 \); using chi-square test). Interestingly, adding this RCT (26) to our meta-analysis would lead to a result that agrees with that of our main analysis, i.e., administration of probiotics protects against VAP (729 patients; fixed effect model: OR, .59; 95% CI, .40–.86; random effects model: OR, .54; 95% CI, .33–.90; data from six trials) (19–23, 26). This fact further bolsters our message.

One might question our choice not to incorporate in our analysis three other RCTs (16–18) that were included in a previous systematic review (24) exploring the role of probiotics in critically ill patients. These three RCTs (16–18) enrolled exclusively postoperative patients who often admitted to the ICU for <48 hrs and underwent MV for <48 hrs; thus, their pneumonia may be not ventilator-associated. This limitation was noted by the authors of the previous review (24). For the present meta-analysis, in an attempt to produce robust results, we adopted a strict approach, i.e., we included only RCT that clearly stated the
enrollment of patients undergoing MV and referred to VAP. Besides, addition of the aforementioned three RCT (16–18) in our meta-analysis would further enhance rather than change our result; probiotics were associated with lower nosocomial pneumonia than control in critically ill patients (859 patients; fixed effect model: OR, .62; 95% CI, .42–.91; random effects model: OR, .61; 95% CI, .39–.95; data from eight trials) (16–23) (Fig. 4).

Another interesting finding of the present meta-analysis is that fewer patients who received probiotics were colonized with *Pseudomonas aeruginosa* compared to controls. This result might explain the fact that incidence of VAP attributable to *Pseudomonas aeruginosa* was found to be lower (albeit not statistically significant) in patients receiving probiotics than controls. This trend toward fewer episodes of VAP attributable to *Pseudomonas aeruginosa* was not seen for other pathogens, namely Enterobacteriaceae and *Staphylococcus aureus*. One could support that these findings (i.e., lower colonization/VAP rates with *Pseudomonas* in probiotic recipients) may reflect a true species-specific effect of probiotics against *Pseudomonas*. However, another could retort that this effect could also be explained if more patients in the probiotic group compared to control group received concurrent antimicrobials with antipseudomonal activity. We could not comment on the accuracy of the latter assumption, given the scarcity of data regarding the previous (i.e., before the diagnosis of VAP) usage of antipseudomonal antimicrobials; in fact, only one eligible RCT reported relevant data there was “no statistically significant relation between *Pseudomonas aeruginosa* infection and prior usage of antipseudomonal antibiotics” (20). Future research on the issue appears to be warranted.

Our review provides additional interesting clues that may be useful for future research on the topic. It seems that probiotic regimens based on lactobacilli may afford benefit in patients undergoing MV; however, we have currently no data regarding the effectiveness of probiotic strains other than lactobacilli, such as yeast. In addition, on the basis of our subgroup analysis demonstrating that a probiotic regimen was protective against pneumonia, one could postulate that administration of combination of probiotics (with prebiotics) instead of individual strains is preferable. Finally, given that two RCT (22, 23) included in our meta-analysis enrolled only trauma patients were positive, one may want to focus on this specific patient population, namely trauma patients, when studying the protective effect of probiotics against VAP.

No episodes of probiotic-associated bacteraemia were encountered in the RCT included in the present meta-analysis and provided relevant information (19, 20, 22). Unfortunately, these RCT (19, 20, 22) did not provide specific data regarding the number of blood cultures obtained by each patient or the proportion of enrolled patients in whom such cultures have been performed. It should be mentioned that probiotics are commercially available as dietary supplements rather than medications; thus, they are not subject to the same strict regulations as other pharmaceutical products (2). This lack of surveillance combined with reports of probiotic-induced diseases, namely *Lactobacillus* VAP (27), bacteraemia (28), and endocarditis (28), raise concerns regarding the safety of probiotics when administered in vulnerable patients, such as those in the ICU, who commonly have some degree of previous immunodeficiency or have severe immunodeficiency develop during their stay in the ICU. However, proponents of probiotics could retort that lactobacilli already have been administered to even more fragile patients, such as transplant recipients (17, 29) and human immunodeficiency virus-positive individuals (30), with no serious complications. Interestingly, in the RCT included in our meta-analysis specifying their exclusion criteria, immunocompromised patients were not eligible (19–21, 23); thus, we could not comment (on the basis of the findings of our meta-analysis) whether probiotics are safe when administered in immunocompromised patients. Experts seem to agree that skepticism about potential toxicity of probiotics should not discourage their study but, rather, vigilance and active surveillance for infections, such as of the bloodstream, is required during the execution of trials using these agents (5, 28).

This study must be viewed in the context of its potential shortcomings. First, one might argue that any attempt to synthesize evidence dealing with probiotics is inevitably limited by the fact that relevant studies often differ on design, clinical condition assessed, and probiotic regimen used (5, 31). For example, a number of trials assessing the effects of probiotics on outcomes of critically ill patients did not report on incidence of VAP (32–34). For this meta-analysis, we considered only RCTs (not contributions with other study design) that clearly referred to VAP (not other diseases); furthermore, all included studies (19–23) used probiotics that were based on lactobacilli. Interestingly enough, the majority of included trials (19, 22, 23) used exactly the same probiotic preparation; a subgroup analysis of them (19, 22, 23) provided a result that was in line with that of our main analysis (i.e., it confirmed the preventive role of probiotics against pneumonia).

Second, because of the paucity of relevant data, the impact of probiotics on ventilator-free days (another common outcome of meta-analyses in VAP) could not be examined. Third, we could not preclude that a proportion of VAP cases might actually be tracheobronchitis rather than pneumonia. Fourth, the eligible RCT (19–23) did not provide adequate information on several issues of the usage of systemic antimicrobials, i.e., their indications, timing of initiation, appropriateness, and average duration of administration. Fifth, differences regarding the dosage, duration, and mode of probiotic administration might act as potential confounders. For this reason, we carefully gathered relevant information from all eligible reports (19–23) and presented it in Table 1. In addition, a subgroup analysis was performed by including only trials in which probiotics were administered via nasogastric/orogastric tube (19, 20, 22, 23); again, probiotics were found to result in fewer episodes of VAP than control.

In conclusion, our study is clinically valuable because it revealed that administration of probiotics leads to lower incidence of VAP than control, a result that could not be generated through the execution of a single trial, given that such trials are often underpowered. On the basis of this finding, we argue that research on the field is promising and should be continued. At least two RCT exploring the effect of probiotics on the incidence of VAP are currently in the recruitment phase (35). The results of our meta-analysis may provide researchers of these trials new perspective in the interpretation of their results and may help other clinical scientists build stronger hypotheses with even better study designs. In such future studies, an adequate number of blood cultures should be collected by each patient receiving probiotics to better-assess their safety.
REFERENCES