**Probiotics for Prevention of Ventilator-Associated Pneumonia**

*To the Editor:*  

We compliment Gu et al* in a recent issue of *CHEST* (October 2012) for their attempt to evaluate the effectiveness of probiotics for the prevention of ventilator-associated pneumonia (VAP) by performing a meta-analysis of randomized controlled trials (RCTs). However, we strongly disagree with the definitive tone of the title of their article. We believe that the limited evidence and several methodologic issues related to their contribution do not justify such strong conclusions.

Firstly, the authors failed to include in their meta-analysis a relevant RCT* that apparently met their inclusion criteria. In that RCT, Tan et al administered probiotics to traumatic brain-injured patients and found that VAP developed in 44% of probiotic recipients vs 68% of control patients. Secondly, Gu et al did not include in their review another relevant RCT (by Spindler-Vesel et al*), arguing that it "provided data on pneumonia, which did not meet the criteria of being ventilator-associated." Their argument is unsatisfactory because that RCT referred to pneumonia that occurred in multiple injured patients under mechanical ventilation hospitalized for at least 4 days in a surgical ICU.* Not surprisingly, this second RCT* was included in previous relevant meta-analyses. Thirdly, one could question the choice of the authors to implement a random effects model despite the fact that they found only low heterogeneity among the included studies. Implementation of a fixed effect model and the addition of the two RCTs* to the meta-analysis would reveal a statistical significance (ie, probiotics decrease the incidence of VAP [pooled OR, 0.74; 95% CI, 0.55-0.98]) (Fig 1). Over the past few months, two additional meta-analyses exploring the role of probiotics in preventing VAP and/or hospital-acquired pneumonia have been published, in addition to the meta-analysis by Gu et al. The more recent revealed that probiotics are beneficial against VAP, whereas the other noted that probiotics are beneficial against hospital-acquired pneumonia (but not against VAP). Revealing or not, a statistical significance in a meta-analysis depends on the choice of included RCTs. However, all recent meta-analyses* and a previous one* agree that the association between the administration of probiotics and the prevention of VAP has, indeed, clinical significance; an approximately 20% decrease in the incidence of pneumonia has been reported consistently. With the previous considerations in mind, we believe that the administration of probiotics may be valuable in managing critically ill patients and that its "condemnation" should be carefully thought out.

**REFERENCES**


**Table 1. Meta-analysis of randomized controlled trials evaluating the effects of probiotics on the incidence of ventilator-associated pneumonia**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Probiotics n/N</th>
<th>Control n/N</th>
<th>OR (fixed)</th>
<th>Weight %</th>
<th>OR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Spindler-Vesel*</td>
<td>4/26</td>
<td>34/87</td>
<td>0.28</td>
<td>0.09</td>
<td>0.89</td>
</tr>
<tr>
<td>Forestier*</td>
<td>24/102</td>
<td>24/106</td>
<td>1.05</td>
<td>0.55</td>
<td>2.00</td>
</tr>
<tr>
<td>Karin*</td>
<td>1/23</td>
<td>3/21</td>
<td>0.27</td>
<td>0.03</td>
<td>2.85</td>
</tr>
<tr>
<td>Knight*</td>
<td>12/130</td>
<td>17/129</td>
<td>0.67</td>
<td>0.31</td>
<td>1.47</td>
</tr>
<tr>
<td>Gamaretos*</td>
<td>15/36</td>
<td>16/36</td>
<td>0.89</td>
<td>0.35</td>
<td>2.27</td>
</tr>
<tr>
<td>Barraud*</td>
<td>23/87</td>
<td>15/80</td>
<td>1.56</td>
<td>0.75</td>
<td>3.25</td>
</tr>
<tr>
<td>Morrow*</td>
<td>13/68</td>
<td>28/70</td>
<td>0.35</td>
<td>0.16</td>
<td>0.77</td>
</tr>
<tr>
<td>Oudhuis*</td>
<td>10/130</td>
<td>9/124</td>
<td>1.06</td>
<td>0.42</td>
<td>2.74</td>
</tr>
<tr>
<td>Tan*</td>
<td>7/16</td>
<td>13/19</td>
<td>0.36</td>
<td>0.09</td>
<td>1.43</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>618</td>
<td>672</td>
<td>100.00</td>
<td>0.74</td>
<td>0.98</td>
</tr>
<tr>
<td>Total events. 109 (Probiotics), 159 (Control)</td>
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<tr>
<td>Test for heterogeneity: Chi² = 13.79, df = 8 (P = 0.09), P = 42.9%</td>
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<tr>
<td>Test for overall effect: Z = 2.09 (P = 0.04)</td>
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</tbody>
</table>

*Figure 1. Meta-analysis of randomized controlled trials evaluating the effects of probiotics on the incidence of ventilator-associated pneumonia. Vertical line = "no difference" point between the two regimens; ■ = OR (the size of each square denotes the proportion of information given by each trial); ♦ = pooled OR for all randomized controlled trials; horizontal lines = 95% CI. df = degrees of freedom.*
REFERENCES


Response

To the Editor:

We thank Drs Siempos and Ntaidou for their interest in our work1 and for their insightful comments. We would like to clarify several important points.

1. We did not include the study conducted by Tan et al2 in our meta-analysis because not all of the patients in the study received mechanical ventilation (16 of 26 in the probiotic group and 19 of 26 in the control group). If this study had been included, the findings would not change, and probiotics do not significantly decrease the incidence of ventilator-associated pneumonia (VAP) (fixed-effects model OR, 0.80; 95% CI, 0.59-1.08).

2. We did not include the trial conducted by Spindler-Vesel et al3 in our review because this study provided data on pneumonia that was not specified as being ventilator associated.

3. The initial title of our article was “Efficacy and Safety of Probiotics in Preventing Ventilator-Associated Pneumonia: A Systematic Review and Meta-analysis of Randomized Controlled Trials.” However, the reviewers believed that the present title would better reflect our findings, and we accepted their suggestion.

4. We initially performed the statistical analyses using a fixed-effects model, with a random-effects model used in cases of significant heterogeneity (P > 50%). However, the reviewers disagreed with such an approach, stating that all meta-analytic studies have heterogeneity and that it is simply a question of whether the study is big enough to find it. They suggested that we use a random-effects model in every case because this would result in a more robust (ie, conservative) analysis. We accepted their insightful suggestions.

5. As for the two recent meta-analyses,4,5 both have their own flaws. The study by Liu et al4 focused on the effects of probiotics on nosocomial pneumonia rather than VAP. In the most recent meta-analysis by Petrof et al5 the data on VAP in their Table 2 and Figure 2 were inconsistent; the data in Table 2 were correct, and the data in Figure 2 were wrong. Reassessment of the data shows that probiotics did not significantly decrease the incidence of VAP (pooled risk ratio, 0.81; 95% CI, 0.59-1.12; P = .2) (Fig 1).

In summary, the current limited evidence precludes final verdicts and strong clinical recommendations. Further research on the use of probiotics for VAP prevention is warranted. Large rigorous multicenter trials will help to generate better estimates of the possible benefits and harm, confirming or refuting the findings from the present analysis.

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