The Use of Probiotics to Prevent Ventilator-Associated Pneumonia in Adults

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INTRODUCTION

- Ventilator-associated pneumonia (VAP) is a type of healthcare-acquired pneumonia that develops after 48 hours of endotracheal intubation.[2]
- VAP is one of the most commonly diagnosed nosocomial bacterial infections in the intensive care unit (ICU).[1]
- VAP may occur from endogenous floral in the oral cavity and upper airway with micro-aspiration around the endotracheal tube cuff.[3]
- VAP prolongs the duration of mechanical ventilation, ICU, and hospital stays, with increased medical costs, morbidity and mortality.[1,4]
- Antibiotic use is one method to attenuate the burden of bacterial colonization but there is concern for development of antibiotic resistance.
- Probiotics have been projected to:
  - Enhance gut barrier function
  - Inhibit colonization of potentially pathogenic microorganisms
  - Maintain a normal intestinal milieu
  - Synthesize antibacterial substances, and
  - Stimulate local immunity.[1]
- Probiotics:
  - Have a high safety profile
  - Have no obvious contraindication or adverse effects
  - Are easily administered, and
  - Are cost effective for patients.[1, 5, 6]
- Studies using probiotics show efficacy in decreasing the length of ICU stays and reducing VAP-related mortality.

PICO AND CLINICAL QUESTION

Population	Hospitalized men and women aged 18 years and above and receiving ≥24 hours of mechanical ventilation
Intervention	Probiotic administration
Comparison	Placebo or no probiotic administration
Outcomes	Acquisition of ventilator-associated pneumonia

Among hospitalized adult men and women, does probiotic administration, as compared to placebo or no probiotic administration, prevent development of ventilator-associated pneumonia?

METHODS

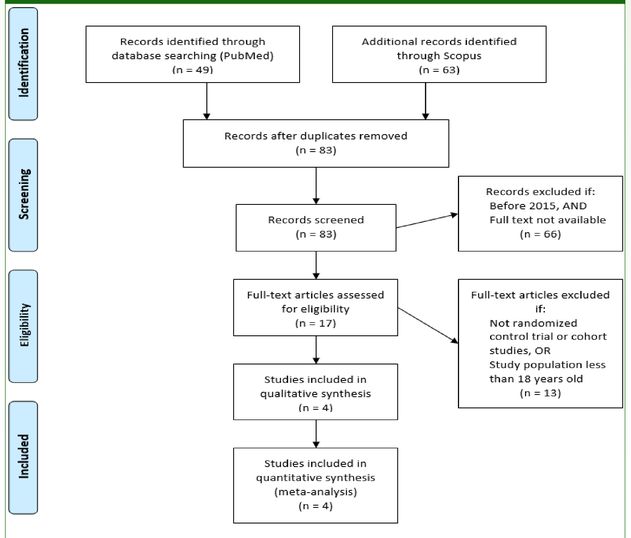

Figure 1. PRISMA flow chart depicting the literature search methodology.

RESULTS

Table 1. An overview of each of the four articles reviewed.
cfu = colony-forming units; VAP = ventilator-associated pneumonia

	Study 1[3]	Study 2[1]	Study 3[6]	Study 4[4]
Study	*Randomized Controlled Study of Probiotics Containing Lactobacillus casei (Shirota strain) for Prevention of Ventilator-Associated Pneumonia.* Rongrungruang et al., 2015	*Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial.* Zeng et al., 2016	*Effect of Probiotics on the Incidence of Healthcare-Associated Infections in Mechanically Ventilated Neurocritical Care Patients.* Kenna et al., 2016	*Effect of a Probiotic Preparation on Ventilator-Associated Pneumonia in Critically Ill Patients Admitted to the Intensive Care Unit: A Prospective Double-Blind Randomized Controlled Trial*. Mahmoodpoor et al., 2018
Objective	To evaluate the efficacy of probiotics, *Lactobacillus casei* (Shirota strain), in reducing the incidence of VAP in medical patients who received mechanical ventilation at Siriraj Hospital in Thailand.	To assess the effectiveness of probiotics *Bacillus subtilis* and *Enterococcus faecalis* in the prevention of VAP when administered by nasogastric tube.	To examine the effectiveness of probiotic administration in the reduction of healthcare-associated infection, including VAP, among medically ventilated neurocritical care patients.	To examine the effectiveness of probiotic administration in decreasing the incidence of VAP in critically ill patients admitted to the surgical intensive care unit.
Study type	Open-label randomized controlled trial	Open-label randomized controlled trial	Prospective cohort study	Double-blind randomized controlled trial
Year published	2015	2016	2016	2018
Sample size	150	235	167	100
Probiotic composition	$8x10^9$ cfu *Lactobacillus casei* (Shirota strain)	$4.5x10^9$ cfu *Bacillus subtilis* $0.5x10^9$ cfu *Enterococcus faecalis*	$1.0x10^8$ cfu *Lactobacillus acidophilus* (gaserri) $1.0x10^6$ cfu *Lactobacillus helveticus* (bulgaricus)	$1.0x10^{10}$ cfu containing *Lactobacillus* (*casei, acidophilus, rhamnosus, bulgaricus*), *Bifidobacterium* (*breve, longum*), *Streptococcus thermophiles* spp
Primary outcomes	Incidence of VAP episodes per 1,000 ventilator-days	VAP incidence Eradication of colonization with potentially pathogenic microorganisms in the oropharynx and stomach	The incidence of hospital-associated infections	VAP occurrence
Statistically significant findings	None	Microbiologically-confirmed VAP reduced in the probiotics group (36.4%) compared to control (50.4%) (p = 0.031) (Table 2) Probability of remaining VAP-free higher in the probiotics group (p = 0.004) (Figure 2) Mean time of VAP onset after endotracheal intubation longer in the probiotic group (10.4 days) compared to control (7.5 days) (p = 0.022) (Table 2)	None	None

Table 2. Incidence of ventilator-associated pneumonia from Study 2.
VAP = ventilator-associated pneumonia

Primary outcome	Probiotics group	Control group	P value
Incidence of clinically diagnosed VAP	48/118 (40.7%)	62/117 (53.0%)	0.059
Incidence of microbiologically-confirmed VAP	43/118 (36.4%)	59/117 (50.4%)	0.031
Patients with gram-negative VAP	27/43 (62.8%)	35/59 (59.3%)	0.866
Patients with gram-positive VAP	7/43 (16.3%)	13/59 (22.0%)	0.603
Patients with *Candida* VAP	1/43 (2.3%)	2/59 (3.4%)	
Time to occurrence of VAP (days)	10.4 ± 2.95	7.5 ± 2.9	0.022

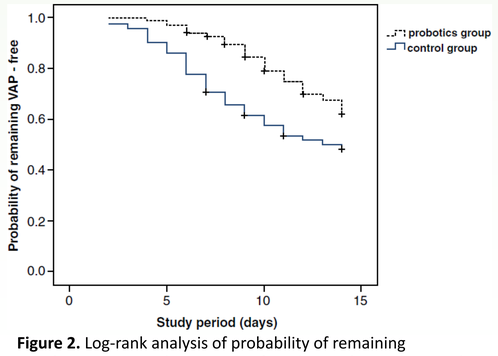

Figure 2. Log-rank analysis of probability of remaining ventilator-associated pneumonia free during the study period from Study 2.

DISCUSSION

- Clinical benefit of probiotic use is still uncertain.
- Studies differ greatly by multiple variables: variety of probiotic strains, individual or combination probiotic strains used, concentrations of probiotics, route of administration (oral cleanse, naso- or orogastric tube), medium used to deliver probiotics (milk product, sterile water, tablet), frequency of administration, additional VAP-prevention techniques.
  - No industry standard for any of these variables.
- Study 1 used LcS and was unique in using a fermentable medium to ideally produce lactic acid in the mouth to kill potentially pathogenic microorganisms.
- Study 2 was the sole study with statistical significance in this review.
  - Concentration: $5.0x10^9$ cfu (90% *B.* subtilis, 10% *E. faecalis*) – less than all other studies (Table 1).
  - Route: enteral feeding (naso- or orogastric tube).
  - Frequency: once daily.
  - *B. subtilis* has been found in other studies to increased secretory IgA which could explain the non-specific reduction in Study 2 (Table 2).[7]
  - Suggests that the choice of strain may be most important (versus higher concentration, route, or frequency of administration).
- Studies 1 and 2 were open-label randomized controlled trials
- Study 3 broadly examined incidence of all healthcare-associated infections with VAP as one end result reviewed.

CONCLUSION

In reviewing the literature, data regarding probiotic use and VAP prevention vary between meta-analyses. Generally, probiotics are of no pathogenic concern and have the potential to aid in immune responses to decrease infectious complications in mechanically-ventilated patients. However, only one of the four studies reviewed was able to show significantly reduced microbiologically-confirmed VAP with the supplementation of probiotics. The three remaining studies were inconclusive in demonstrating efficacy of probiotics. The significant variance among study strains, concentrations, administration routes, administration frequency, and VAP-prevention bundles used throughout the four studies made comparisons of study outcomes difficult to determine. Further research is needed to determine the efficacy of probiotics in the clinical care and prevention of VAP.

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