PROBIOTICS FOR THE PREVENTION OF VENTILATOR-ASSOCIATED PNEUMONIA

Ventilator-associated pneumonia (VAP) is a nosocomial infection that remains a leading cause of morbidity and mortality in critically ill patients. Rising rates of antimicrobial resistance have shifted the focus from treatment to prevention strategies for VAP. One investigated prevention agent is probiotics. Probiotics are theorized to delay or prevent VAP by inhibiting oropharyngeal and gastric colonization of pathogens. Probiotics have been studied for the prevention of VAP, but the results are inconsistent. Some studies were weak in that they failed to differentiate VAP from other types of hospital acquired pneumonia or use appropriate diagnostic criteria. This issue of CLIPS briefly summarizes an article that reviews the published data regarding the safety and efficacy of probiotic use in preventing ventilator-associated pneumonia. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Ventilator-Associated Pneumonia

- VAP is defined as pneumonia occurring more than 48 hours after endotracheal intubation and represents the leading hospital-acquired infection in the United States.
- VAP is associated with increased duration of mechanical ventilation, longer intensive care unit (ICU) and hospital stays, and excessive health care costs.
- Mechanically ventilated patients are at an increased risk of developing colonization of the lower respiratory tract due to the epithelial damage to the oropharynx and/or trachea that can occur during intubation. In addition, bacterial entry via the endotracheal tube cuff or microaspiration is more common in these patients.
- The most common causative organisms are aerobic gram negative bacteria, but multi-drug resistant bacteria like *Pseudomonas aeruginosa*, *Acinetobacter* spp., and methicillin-resistant *Staphylococcus aureus* becoming more prevalent.
- No standard diagnostic criteria for VAP exist; however, diagnosis of VAP includes a combination of clinical suspicion and physical examination, radiographic, and microbiological evidence.

Probiotics

- Probiotics are living microorganisms that may be associated with a health benefit when administered in adequate amounts.
- Probiotics are promoted to maintain microbial balance within the host organism.
- Probiotics include both bacterial and yeast formulations and are often strains of bacteria that are ubiquitous in the human flora.
- Strains of lactobacilli, bifidobacteria, and *Saccharomyces* spp. are most commonly found in the products.
- After ingestion, probiotics colonize in the gut and are thought to promote gastrointestinal integrity and modify intestinal flora through various antimicrobial effects. Both mechanisms may have benefit in VAP prevention by decreasing or changing oropharyngeal colonization.

Methods and Study Selection

- A PubMed database search from January 2000 to August 2011 was conducted using the search terms probiotics, synbiotics, and ventilator-associated pneumonia.
- The search was performed to identify original reports of probiotic use for the prevention of VAP.
- Two pilot studies, three randomized controlled trials, and one meta-analysis were found that addressed probiotic use for VAP prevention and were analyzed in the review.
- The studies were an in-patient setting, and used mechanically ventilated patients as the study population with the exception of a small pilot study that used patients in ICU and a controlled clinical trial that used patients expected to require mechanical ventilation within 72 hours.

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Methods and Study Selection (continued)

- Each study used a different probiotic formulation as the intervention. Three utilized strains of *Lactobacillus*, one used Synbiotic 2000 FORTE, and one trial used 5 Ergyphilus, which is a multi-species probiotic product. Each gave the probiotic formulation twice daily by various routes. All of the trials compared the probiotic products with placebo except a pilot study that used chlorhexidine 0.1% solution as the control.

Results

- The studies showed mixed results regarding the beneficial effect of probiotics for VAP prevention. Only two studies found statistically significant benefits of probiotic use.
  - One pilot study found that the probiotic group showed a significant delay in acquisition of respiratory aspirates compared to placebo, but an insignificant effect in VAP incidence.
  - A controlled clinical trial using *Lactobacillus rhamnosus* GG $2 \times 10^9$ CFU found a significant difference in VAP incidence with probiotic use compared to placebo (9.1% vs. 40% $p=0.007$), and the time to onset of VAP was delayed with probiotic use.
- Most of the trials had methodological flaws and limitations that included insufficient sample size, extensive exclusion criteria, single center design, and the selection of high risk patients. One trial was stopped early before the required sample size was met due to safety concerns raised in a trial examining the use of probiotics in patients with acute pancreatitis.
- In contrast, the meta-analysis found favorable and statistically significant results for probiotic use in VAP prophylaxis. The analysis of five different trials found the incidence of VAP was significantly decreased in probiotic treated patients as compared to the control groups.
  - The odds ratio for development of VAP in the fixed-effect model was found to be 0.61 (95% CI 0.41 to 0.91) and in the random-effects model 0.55 (95% CI 0.31 to 0.98).
  - The limitations of the meta-analysis include lack of data regarding concurrent antibiotic administration, inclusion/exclusion criteria bias, and differences in design and results between the trials.

Probiotic Safety Issues

- Probiotics are considered generally safe and well tolerated.
- Probiotics are classified as dietary supplements; therefore, they have less rigorous requirements than prescription drug products for safety, efficacy, and purity.
- Labeling studies have concluded that some probiotic products have improperly identified organisms in them and discrepancies in the actual numerical content of organisms compared to what is labeled.
- Probiotics are live organisms so they have the potential to induce systemic infections in some individuals.
- Most cases of severe infection occurred in immunocompromised, chronically diseased or debilitated patients.
- Use of probiotics may result in antibiotic-resistance; however, the risk of this adverse effect has not been elucidated.
- Individual probiotics, mainly *Lactobacillus*, do have evidence of safety in certain populations, including pregnant women, premature infants, hospitalized children, immunosuppressed adults, and the elderly.
- In the reviewed trials and studies, no adverse events with probiotic use for VAP prevention were reported. The studies found no evidence of bacteremia, pneumonia, or bowel ischemia due to probiotics.
- Caution is advised with probiotic use. The studies evaluated used extensive exclusion criteria in their design.

Conclusion

- Clinical trials failed to demonstrate a clear benefit with the use of probiotics in mechanically ventilated patients.
- The evaluated trials differed with regards to the probiotic species used, route and mode of administration, VAP diagnostic criteria, and the population used in the study.
- Different sampling techniques, sites, and frequency in the assessment of colonization rates were documented.
- Study design differences may account for the lack of clear evidence that support the use of probiotics in VAP prevention.
- Future study designs need to be standardized according to VAP diagnostic criteria, probiotic species used, probiotic administration and study population.
- Despite some promising data, the results of studies do not support the use of probiotics as a prophylactic strategy for ventilator-associated pneumonia at this time.

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