Intensive Care Med (2016) 42:1182–1184
DOI 10.1007/s00134-016-4353-0

EDITORIAL

Evidence in the eye of the beholder: about probiotics and VAP prevention

Stijn Blot[1,2*], Antonio Torres[3,4] and Bruno Francois[5]

Ventilator-associated pneumonia (VAP) remains an important source of morbidity and therefore avoiding this complication continues to be a priority in terms of patient safety and quality improvement [1]. A variety of VAP prevention measures are available and include strategies targeting bacterial translocation, biofilm formation, micro-aspiration of subglottic secretions, reduction of exposure time, and modulation of colonization [2–4]. Regarding the last of these, in the past decades, the use of probiotics has come to the front. Probiotics are generally defined as living organisms that—when ingested in adequate amounts—provide health benefits to the host [5]. In the past two decades, probiotics have increasingly been considered as an effective and safe approach to improve gastrointestinal barrier function, modification of the gut flora (i.e., avoiding colonization with potential pathogenic microorganisms, PPMOs), and immunomodulation [6]. Although results appear to be variable according to the index population, various benefits have been described for either critically and non-critically ill patients, including prevention of *Clostridium difficile*-associated diarrhea, prevention of infectious complications in patients with severe acute pancreatitis, post liver transplantation, and following major abdominal surgery. Also, step by step, the evidence is accumulating for the use of probiotics in the prevention of VAP. In a recent article in *Intensive Care Medicine*, Zeng et al. report on an open-label randomized multicenter study to assess the efficacy of the administration of a probiotic capsule containing active *Bacillus subtilis* and *Enterococcus faecalis* to prevent VAP [7]. The intervention group received the capsule thrice daily for 2 weeks in addition to standard precautions for VAP prevention. The control group received standard measures to prevent VAP. Two hundred and fifty patients were randomized and 235 completed the study, of which 118 were in the intervention arm. In brief, a significant reduction in microbiologically confirmed VAP was demonstrated (36.4 vs. 50.4 %; $p = 0.031$), but not in clinically suspected VAP (40.7 vs. 53.0 %; $p = 0.059$). The latter is probably the reason why probiotics neither resulted in a reduction of antimicrobial consumption nor in a shortening of ICU and hospital stay. Acquisition of PPMOs in the stomach was lower in the intervention group (24 vs. 44 %; $p = 0.004$), but no difference was observed in acquisition of PPMOs in the oropharynx, and no differences were noted in rates of eradication of PPMOs in either the oropharynx or the stomach.

These new data need to be interpreted with caution. Firstly, the baseline incidence of VAP in the ICUs was very high according to the low overall severity of illness and mortality. This might be the result of poor infection control practices and a less strict diagnostic approach for VAP not based upon an invasive technique and using semiquantitative bacterial counts. Most probably the lenient VAP definition resulted in a misclassification of tracheobronchitis cases into pneumonia. In the area of prevention using a definition covering a broader spectrum of respiratory infections can be justified, but when doing so the wording should be properly adapted (i.e., not all respiratory infections can be designated as VAP). In this regard, the development of prevention-specific definitions of respiratory infections can be advocated. Also, a high baseline VAP rate and limited adherence to VAP prevention measures make the trial vulnerable to a Hawthorn effect, given the open-label study design. Finally, with the exception of radiological findings, VAP diagnosis was not blinded for treatment allocation; a blinded approach to VAP diagnosis could have, at least partially, countered the bias generated by the open-label strategy.

*Correspondence: stijn.blot@ugent.be
[1] Department of Internal Medicine, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium
Full author information is available at the end of the article

Springer

Table 1 Protocol for probiotics use based on the available scientific evidence [6]

Item	Translation into practice
Patient selection	Indicated disease stats include liver transplantation, major abdominal surgery, trauma, pancreatitis, and *Clostridium difficile*-associated diarrhea. Relative contraindications include immunosuppression and cardiac valvular disease
Timing related to illness	In the presence of an (anticipated) indication, probiotics are to be initiated as soon as possible
Type of preparation	Commercially prepared formulations are preferred to home-made preparations because of limited data on the latter
Dose and route of therapy	Enteral administration of $\geq 5 \times 10^9$ colony-forming units/day; oropharyngeal swabbing with probiotics can be considered in intubated patients [10, 11]
Duration of therapy	14–21 days
Handling	Strict hand hygiene (including the use of gloves) of healthcare workers when handling probiotics is warranted. Opening capsules is to be avoided in the patient area and is done preferably in the pharmacy department to avoid aerosolization of spores and contamination of sterile sites

Taking into account these limitations, can this study be considered a step in favor of using probiotics to prevent VAP? This study adds to the existing literature summarized in a meta-analysis that demonstrated an overall reduction in infectious complications and VAP [8]. However, when exclusively higher-quality trials were pooled, the favorable outcomes disappeared. Contrariwise, the beneficial effects were obvious in trials with an inherent high risk of bias [8]. In the same line, the present study by Zeng et al. seems to be yet another non-blinded trial reporting tight statistical significance ($p = 0.03$).

Besides the variable scientific evidence, too many responses remain unanswered, thereby hampering the widespread adoption of probiotics in daily practice. First, if the mechanism of action of probiotics is mainly based on immunomodulation and preventing potentially harmful colonization, how can the beneficial effects appear at such an early stage? Second, there is the fear that probiotic administration might spread resistance genes from probiotic bacteria to normal gastrointestinal gut flora. However, resistance genes of probiotics are characteristically not plasmid-bound, thereby hampering transfer to other species [6]. To clear this issue up, an expansive and long-term cluster randomized study is needed, rather than a study randomizing selected cases. In the Zeng study, 457 patients were assessed for eligibility in 11 ICUs over a 5-year period, giving an average inclusion of about 8 patients per center per year. At such an inclusion rate, a study can never be capable of accounting for changes in microbial ecology, either favorable or deleterious. Thirdly, there is the issue of patient safety. Case reports of probiotics-related sepsis have been described in high-risk patients. The wide variation in type of active bacteria administered hampers a clear view of the safety of probiotics as a whole. Nevertheless, overall, on the basis of the trials available, probiotics can be considered as safe. Anyhow, safety monitoring with the use of probiotics is advocated [9]. Finally, there is huge heterogeneity in the types of probiotics used and dosing schemes [6, 8]. Therefore, defining clear recommendations regarding their use remains complex. On the basis of the currently available evidence, Urben et al. [6] proposed a protocol for the use of probiotics (Table 1). As for the near future it remains to be determined whether a protocol considering these elements provides the expected outcomes while minimizing the risks for the individual patient and for the microbial ecology.

Author details
[1] Department of Internal Medicine, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium. [2] Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia. [3] Pulmonary Intensive Care Unit, Respiratory Institute, Hospital Clínic of Barcelona, Barcelona, Spain. [4] IDIBAPS and CIBERES, Barcelona, Spain. [5] Inserm CIC 1435, Inserm UMR 1092 and Reanimation Polyvalente, CHU Limoges, Limoges, France.

Acknowledgments
SB holds a research mandate of the Special Research Fund at Ghent University.

Compliance with ethical standards

Conflicts of interest
All authors: no conflict of interest.

Received: 4 April 2016 Accepted: 5 April 2016
Published online: 13 April 2016

References

1. Lorente L, Blot S, Rello J (2010) New issues and controversies in the prevention of ventilator-associated pneumonia. Am J Respir Crit Care Med 182:870–876. doi:10.1164/rccm.201001-0081CI
2. Lizy C, Swinnen W, Labeau S et al (2014) Cuff pressure of endotracheal tubes after changes in body position in critically ill patients treated with mechanical ventilation. Am J Crit Care 23:e1–e8. doi:10.4037/ajcc2014489
3. Morrow LE, Gogineni V, Malesker MA (2012) Probiotic, prebiotic, and synbiotic use in critically ill patients. Curr Opin Crit Care 18:186–191. doi:10.1097/MCC.0b013e3283514b17
4. Blot SI, Poelaert J, Kollef M (2014) How to avoid microaspiration? A key element for the prevention of ventilator-associated pneumonia in intubated ICU patients. BMC Infect Dis 14:119. doi:10.1186/1471-2334-14-119
5. Food and Agricultural Organization of the United Nations/World Health Organization (2002) Guidelines for the evaluation of probiotics in food. Working group report 2002. FAO/WHO, Rome

6. Urben LM, Wiedmar J, Boettcher E et al (2014) Bugs or drugs: are probiotics safe for use in the critically ill? Curr Gastroenterol Rep 16:388. doi:10.1007/s11894-014-0388-y
7. Zeng J, Wang C, Zhang F-S et al (2016) Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. Intensive Care Med. doi:10.1007/s00134-016-4303-x
8. Petrof EO, Dhaliwal R, Manzanares W et al (2012) Probiotics in the critically ill: a systematic review of the randomized trial evidence. Crit Care Med 40:3290–3302. doi:10.1097/CCM.0b013e318260cc33
9. Snydman DR (2008) The safety of probiotics. Clin Infect Dis 46 Suppl 2:S104–S111. doi:10.1086/523331 **(discussion S144–51)**
10. Morrow LE, Kollef MH, Casale TB (2010) Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med 182:1058–1064. doi:10.1164/rccm.200912-1853OC
11. Klarin B, Molin G, Jeppsson B, Larsson A (2008) Use of the probiotic Lactobacillus plantarum 299 to reduce pathogenic bacteria in the oropharynx of intubated patients: a randomised controlled open pilot study. Crit Care 12:R136. doi:10.1186/cc7109