

Probiotics in the intensive care unit

Lee E. Morrow

Creighton University Medical Center, Division of Pulmonary, Critical Care and Sleep Medicine, Omaha, Nebraska, USA

Correspondence to Dr Lee E. Morrow, MD, MSc, Associate Professor of Medicine, 601 North 30th Street, Suite #3820, Omaha, NE 68131, USA
Tel: +1 402 449 4486; fax: +1 402 449 4925;
e-mail: lmorrow@creighton.edu

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Purpose of review

To examine current knowledge regarding the utility of probiotics in a variety of medical conditions afflicting critically ill patients in the intensive care unit (ICU).

Recent findings

Recent experimental and clinical studies have furthered our understanding regarding the use of probiotic therapy across various clinical conditions. These disorders include antibiotic-associated diarrhea, *Clostridium difficile*-associated diarrhea, acute pancreatitis, ventilator-associated pneumonia, and sepsis among others. Although each of these conditions is germane to ICU patients, few studies have specifically studied this vulnerable population. The current data supporting the use of probiotics in the treatment of these different clinical conditions consist mostly of the results of small, single-center trials with varying quality of research design. Although recent studies have also generally demonstrated favorable results, one well designed study in severe pancreatitis found increased mortality with probiotic therapy. These results emphasize the need for improved data regarding mechanisms of action as well as rigorous attention to safety monitoring during the execution of probiotic clinical trials.

Summary

Data supporting the use of probiotics in different clinical conditions are variable in scope and quality. Large, well designed, randomized, multicenter trials are needed to better define the role and safety of probiotics in critically ill patients.

Keywords

hospital-acquired infection, nutrition, probiotics

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Introduction

Probiotics are commercially available microorganisms which, when ingested as individual strains or in combinations, offer potential health benefits to the host. These agents are often concurrently administered with substances that promote bacterial colonization and growth (prebiotics): in this instance, they are referred to as synbiotics. Because probiotics are marketed as nutritional supplements or dietary aids – and not as pharmaceuticals – they have not been subjected to the rigorous evaluation and oversight of the Food and Drug Administration (FDA). Accordingly, data supporting probiotic use in some disease states are limited in scope and quality. Research on probiotic therapy has surged as recent trends in antimicrobial resistance have heightened awareness of our need for nonantibiotic approaches to prevention and treatment of nosocomial infections.

Antibiotic-associated diarrhea

Antibiotic-associated diarrhea (AAD) occurs in approximately 25% of patients receiving antimicrobial agents. Patients with AAD are at increased risk of developing nosocomial infections and have increased mortality.

Prevention of AAD is one of the most investigated areas for the role of probiotics. There are currently five meta-analyses of trials of probiotics for AAD [1–5]. Although variable in magnitude, each of these studies showed an overall reduction in the risk of AAD with probiotic administration.

In the largest meta-analysis to date, McFarland evaluated 25 randomized controlled trials of probiotics for the prevention of AAD that included 2810 patients. In this analysis, the collective relative risk for AAD in these 25 studies was 0.43 (95% confidence interval 0.31–0.58), suggesting a significant protective effect of probiotics against AAD [5]. Included studies used many different probiotic strains – including several combination products – at various doses. Using stratification by probiotic strain, only *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii*, and combination products reliably reduced AAD. Although the duration of probiotic use did not appear to make a difference, higher doses of probiotics were generally associated with efficacy.

A more recent randomized, controlled clinical trial evaluated the efficacy of a commercially available yogurt

containing *Lactobacillus casei* Immunitas, *Saccharomyces thermophilus*, and *Lactobacillus bulgaricus* [6]. The study cohort of 135 patients was randomized to twice-daily yogurt shakes containing probiotics or placebo at the time of starting antibiotic therapy. There were significant reductions in the incidence of AAD and *C. difficile*-associated diarrhea (CDAD) in the probiotic-treated group. Probiotic therapy reduced the odds of AAD by 75%, and no adverse events were reported.

Another randomized, placebo-controlled clinical trial compared the utility of a fermented milk product containing multiple probiotics (*L. rhamnosus* GG, La-5, and *Bifidobacterium lactis* Bb-12) to a comparable product containing heat-killed probiotic agents [7]. In this smaller study of only 63 patients, AAD was significantly less in the probiotic study arm (5.9 vs. 27.6%). The relative risk of developing AAD was 0.21 if treated with the probiotic milk drink. Cumulatively, these data suggest that probiotics are effective in preventing AAD. However, no study to date has focused exclusively on critically ill patients.

***Clostridium difficile*-associated diarrhea**

CDAD is a less common but more severe side effect of antibiotic therapy. Recent epidemics of a hyper-virulent *C. difficile* strain have demonstrated significant morbidity and mortality, highlighting the need for better prevention and treatment of CDAD. Metronidazole and vancomycin are the antibiotics most commonly used to treat CDAD. Recent studies using metronidazole in severely ill patients show response rates of 62–78%, a significant decline from historic response rates of 95% [8–10]. Accordingly, many clinicians change from metronidazole to vancomycin if there is no clinical improvement after 72 h of therapy. A recent study has suggested that vancomycin is superior to metronidazole in the treatment of patients with severe CDAD [11].

To date, there are limited data on the prevention and treatment of CDAD using probiotics. A systematic review by Dendukuri *et al.* [12] identified only four studies on the prevention or treatment of CDAD or both. Of these, one study evaluated probiotic prevention of CDAD [13]. In this trial, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* led to slightly lower rates of *C. difficile* toxin-positive cases. However, the very small numbers of patients preclude definitive conclusions. Five related studies of AAD prevention included data on the prevention of CDAD and were reviewed. Again, issues with small sample sizes limited conclusions, but there was no clear suggestion of benefit with probiotics.

The three remaining studies in the Dendukuri review focused on CDAD treatment: one studied *Lactobacillus plantarum* and two assessed *S. boulardii* [14–16].

Although each of these studies was inconclusive, subgroup analyses suggested potential efficacy in patients with a history of CDAD or in those on high-dose vancomycin therapy. The only recent study on the efficacy of probiotics in patients with recurrent CDAD did not show benefit with *Lactobacillus* GG [17]. Although these results are consistent with prior studies in recurrent CDAD, all of the existing evaluations are badly underpowered.

Acute pancreatitis

Approximately 20% of patients with acute pancreatitis will develop necrotizing pancreatitis. This subset of patients has a mortality rate of 10–30%, which is mainly attributable to infectious complications. These infections are believed to occur as a result of small bowel bacterial overgrowth, mucosal barrier failure, and translocation of intestinal organisms. Because antibiotic prophylaxis with severe pancreatitis has failed to show clinical benefit, probiotic prophylaxis has been studied in some detail.

Several older studies that evaluated the efficacy of probiotic prophylaxis in patients undergoing abdominal operations and pancreatitis showed reductions in infectious complications. However, these studies had small sample sizes, were fraught with methodologic issues, and ultimately have not led to significant use of probiotic therapy in these patients.

A recent randomized, double-blind, placebo-controlled, multicenter clinical trial by Besselink *et al.* [18**] rigorously assessed the utility of a novel, multispecies probiotic product in patients with severe pancreatitis. A total of 296 patients were randomized to receive 28 days of therapy with enteral probiotic therapy or placebo. These investigators found that though infectious complication rates were not significantly different between the two study groups (30% in probiotics vs. 28% in placebo), mortality rates were significantly higher in the probiotic study (16%) than in the placebo arm (6%). Further investigation determined higher rates of bowel ischemia in the probiotic patients (6 vs. 0%).

The present study stimulated significant discussion of the role of probiotics in acute pancreatitis as well as the safety of administering probiotics to critically ill patients. The lack of a mechanism directly linking probiotic administration with bowel ischemia and the novel probiotic preparation used in the Besselink study has ultimately resulted in more confusion regarding probiotic therapy in pancreatitis patients. However, a subsequent meta-analysis of four randomized, controlled clinical trials of probiotics in severe acute pancreatitis (including the Besselink study) showed that enteral feedings supplemented with probiotics did not significantly influence mortality – favorably or adversely [19].

Ventilator-associated pneumonia prophylaxis

Although selective digestive tract decontamination in critically ill patients has been shown to reduce ventilator-associated mortality, it is also associated with increased rates of antimicrobial resistance. Accordingly, it is not routinely used at most centers. The use of probiotics to preserve or reestablish normal gut microflora has been proposed as an alternative to selective digestive tract decontamination in critically ill patients. This idea stems from a study of healthy participants, in which consumption of a fermented milk product containing probiotics resulted in a significantly higher rate of pathogenic bacteria elimination from the nasal cavity when compared with consumption of a placebo yogurt drink [20]. Pathogens removed from the upper airways included *Staphylococcus aureus*, *Streptococcus pneumoniae*, and beta-hemolytic streptococci.

A subsequent study by Forestier *et al.* [21*] demonstrated that oral administration of a probiotic *Lactobacillus* preparation delayed respiratory tract colonization with *Pseudomonas aeruginosa*. This delay in colonization resulted in a reduced rate of ventilator-associated pneumonia caused by *P. aeruginosa* in the probiotic-treated patients. Despite theoretic plausibility and the results of this study, equipoise remains regarding the ability of probiotics to reduce nosocomial pneumonia rates [22].

Sepsis

The gastrointestinal system appears to play a key role in the pathogenesis of sepsis and multisystem organ dysfunction syndrome (MODS) owing to a breakdown of intestinal barrier function with resulting increased bacterial translocation into the systemic circulation. The efficacy of probiotics in preventing sepsis and MODS has been evaluated in critically ill patients with traumatic injuries, acute severe pancreatitis, in those undergoing surgery, and in the post-liver transplant period [23–25]. Kotzampassi *et al.* [23] treated critically ill trauma patients with a commercial probiotic product for 15 days in a randomized clinical trial. Probiotic-treated patients had significantly reduced infection rates, sepsis events, intensive care unit (ICU) length of stay and mortality [23]. Olah *et al.* [24] showed that severe sepsis patients administered the same product had reduced incidence of systemic inflammatory response syndrome and multiorgan failure. Spindler-Vesel *et al.* [25] also demonstrated reduced infection rates in trauma patients treated with this combination of probiotics and prebiotics.

Urinary tract infections

Clinical trials to date have evaluated probiotics for prevention and treatment of urinary tract infections (UTIs). Probiotic administration has been via oral ingestion, direct bladder injection, and vaginal suppository. Results from the studies on UTI prophylaxis vary in the

strength of their conclusions based on sample size and the probiotic strain used. However, existing clinical trials using *Lactobacillus* species have generally favorable results. Data on UTI treatment are limited to a very small number of studies using intravesicular administration of probiotics to patients with neurogenic bladders. Probiotic strains have been unsuccessful in establishing bladder colonization and therefore require repeat administration [26]. Accordingly, this practice has been abandoned.

Others

Multiple other areas with potential implications for critically ill patients have been studied in varying levels of detail. These disease states include hematopoietic stem cell transplant, irritable bowel syndrome, *Helicobacter pylori* infection, asthma, atopic disease and eczema, food allergies, liver cirrhosis, diverticular disease, and prevention of wound infections. None of these disease states currently has adequate data to allow meaningful assessment of probiotics' relative efficacy and safety. Data regarding these conditions in the critically ill population are even less rigorous.

Safety

Because probiotics are 'natural' products, they are presumed by many to be harmless adjuncts to enteral nutrition. However, probiotics are commercially marketed as dietary supplements or digestive aids and not as pharmaceutical products. This unique perspective not only limits the health claims that can be made by manufacturers, but also minimizes their oversight by the FDA. As a result, rigorous documentation of consistency in manufacturing, efficacy, and safety is also limited. The Code of Federal Regulations title 21 details the allowed uses of microorganisms in food [27]. These rules comment on the incorporation of bacteria into food production but do not specifically comment on probiotic uses of active cultures. Many probiotic supporters erroneously believe that probiotics fall into the Generally Recognized as Safe (GRAS) category of food additives by default. However, such classification involves a lengthy review process by the FDA, and there are no legal requirements for companies to interact with the FDA regarding GRAS substances. Note that approval of GRAS status only evaluates safety; clinical benefits are not assessed. To date, relatively few probiotic agents have been the subjects of GRAS notices.

Potential safety issues with probiotic administration involve probiotic-induced disease, transfer of antibiotic resistance, and toxic or metabolic effects. Epidemiologic studies incorporating longitudinal usage data suggest no increase in risk at the population level. However, these studies have limited applicability to the critically ill patient. Case reports linking probiotic administration

to endocarditis and bacteremia/fungemia exist but are remarkably uncommon. Other vulnerable patient populations in which probiotic safety has been demonstrated include pregnant women, premature neonates, bone marrow transplant patients, and solid organ transplant recipients [28^{*}]. Although the vast majority of the studies discussed in this review have demonstrated safe use, the surprising findings of the Besselink study in pancreatitis remind us of the need for commitment to data-safety monitoring boards as our research efforts move forward.

Conclusion

Recent clinical trial results regarding the use of probiotics in treating critically ill patients are compelling and merit further study. Although a recent systematic review showed no evidence to support the use of probiotics in the adult ICU, the inclusion of studies with various diseases and different probiotics limits the applicability of these authors' conclusions [29^{*}]. As evidence for efficacy emerges across multiple indications, it is clear that the success of any probiotic agent in one clinical setting does not guarantee a similar response in another [30]. Well designed, large-scale, multicenter trials that follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines are needed [31]. Issues complicating the interpretation of currently available studies include lack of quality control; use of different species, strains, doses, and combinations; and significant deficiencies in study designs. The most significant gap in our current knowledge regarding probiotics is their mechanism(s) of action.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 175–176).

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