

Probiotic Use in the Critically Ill Patient

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BACKGROUND

With more than 400 bacterial species and up to 10^{11} organisms per mL of feces, the human gastrointestinal (GI) tract is teeming with microbial inhabitants.¹ Under normal conditions, bacterial colonization of the intestine does not cause illness. In fact, the resident microflora inhibits the overgrowth of potentially pathogenic bacteria.¹ However, during critical illness, the intestinal environment changes drastically. Differences in osmolality, pH, oxygen concentration, and nutrient availability may result from administration of vasopressors, artificial nutrition, and opiates, as well as the patient's stressed state.² Additionally, changes that create a hostile environment for intestinal microflora include gut ischemia, decreased GI motility, and antibiotic administration.² These alterations in local milieu caused by critical illness allow the composition of the GI microflora to shift, possibly leading to colonization of the nasopharyngeal and gastrointestinal mucosa with potentially pathogenic organisms, predisposing the patient to pneumonia and sepsis.³⁻⁵

Bacterial infections and multiorgan failure are often the cause of increased morbidity and mortality in critically ill patients. Frequently, these infections are caused by gut-derived microorganisms.⁶ It is postulated that during critical illness, the breakdown of the GI barrier may promote translocation of both bacteria and bacterial components such as endotoxins from the intestinal lumen to extra-intestinal sites such as the bloodstream, lymph nodes, and liver.^{5,7} Both the proliferation and translocation of pathogenic organisms may stimulate immune responses leading to increased intestinal permeability and inflammation. This creates a vicious cycle of immune dysfunction that can eventually result in septic complications and multiple organ failure. Probiotics may attenuate this downward spiral through various mechanisms.

MECHANISMS OF ACTION

A probiotic is defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host."⁸ Prebiotics are non-digestible food supplements that selectively promote the growth of colonic bacteria. When pre- and probiotics are used in combination, they are termed synbiotics.⁹ Probiotics can decrease colonization of the intestine by pathogenic organisms through competitive inhibition.⁷ To prevent the adhesion of pathogens to the intestinal epithelium, some probiotics produce mucin, which stimulates the production of mucus to form a protective barrier, while others adhere to the intestine better than their microflora counterparts.¹⁰ Probiotics also produce bacteriocins, hydrogen peroxide, biosurfactants, and defensin to antagonize the survival of pathogenic bacteria and improve intestinal barrier function.¹¹

In addition to microbiological effects, probiotics are thought to influence mucosal immune response. Pathogenic components such as lipopolysaccharide, flagellin, and lipoteichoic acid are recognized by pattern recognition molecules, toll-like receptors (TLR).¹² Activation of these receptors stimulates the production of proinflammatory cytokines and triggers the nuclear factor κ B (NF- κ B) pathway. However, recognition of commensal intestinal microflora induces anti-inflammatory cytokine, secretory IgA and IgG production, inhibits the effects of the proinflammatory NF- κ B pathway, and activates the production of epithelial repair factors.¹² These various immunological effects are possible mechanisms by which probiotics help regulate intestinal inflammation.

continued

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Many different microorganisms have been studied as probiotics. The most evaluated include *Streptococcus thermophilus*, *Saccharomyces* species, and various species of lactobacilli and bifidobacteria. Probiotics vary greatly in their characteristics such as size, resistance to antibiotics, and optimal growth conditions. Furthermore, the effects of probiotics tend to be strain-specific. As a result, the observed benefits of therapy from a particular species cannot be generalized to other probiotic species.

CLINICAL STUDIES IN THE CRITICALLY ILL

The use of probiotics has been investigated for a diverse range of indications. There is evidence of the efficacy of probiotics for the prevention and treatment of acute diarrhea, antibiotic-associated diarrhea, and atopic dermatitis.¹³⁻²⁰ Other applications with ongoing research include inflammatory bowel disease, colon cancer, ulcerative colitis, and dental caries. However, many of these studies were performed in medically stable patients and research in the critically ill is limited.

A meta-analysis that evaluated 8 randomized controlled trials of pre-, pro-, and synbiotics in 999 adult intensive care unit (ICU) patients found that the risk for mortality, ICU length of stay, and incidence of nosocomial infections and pneumonia was not significantly different.²¹ A limitation of this meta-analysis is the inclusion of studies with diverse patient groups in whom the effect of probiotics may differ. Additionally, the probiotic intervention varied among included studies. Since probiotic effect is species-specific, the variability of the probiotic interventions in the studies included in this meta-analysis may preclude detection of differences in measured outcomes.

A separate review that evaluated probiotic use in patients with nosocomial infections or those undergoing major surgery confirmed that current evidence does not support the use of probiotics in the restoration of normal human flora in critically ill patients.²² The authors specifically evaluated the use of probiotics in *Clostridium difficile*-associated diarrhea and hospital-associated pneumonia. Similar to the meta-analysis mentioned above, the clinical trials evaluated in this review contained a diverse set of probiotic strains, study endpoints, and patient populations, which yielded conflicting results and made the data difficult to interpret.

In a more recent randomized, double-blind, placebo-controlled trial of patients admitted to the ICU, patients who received 2 sachets daily of a mixture of probiotics (4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium* and *Streptococcus salivarius* subsp *Thermophilus*) had a greater enhancement of immune activity as shown by larger increases in systemic IgA and IgG concentrations compared to those who received placebo or sonicates (heat inactivated bacteria) ($P < 0.05$ for both).²³ There were no significant differences in multiple organ dysfunction syndrome (MODS) scores or number of days in the ICU between the groups.²³

In an interim analysis (60% of calculated sample size [$n=65$]), a prospective, randomized, double-blind, placebo-controlled trial of a synbiotic (4 probiotics [*Pediococcus pentoseceus*, *Leuconostoc mesenteroids*, *L. paracasei*, and *L. plantarum*] with inulin, oat bran, pectin, and resistant starch) in severe multiple trauma patients admitted to the surgical ICU, reported a significant reduction in the rate of infection, septic complications, days on mechanical ventilation, and length of stay in the ICU ($P < 0.05$ for all).²⁴ Although these results are intriguing, definitive conclusions cannot be drawn until the final outcomes of the study have been published.

More recently, Probiotic Prophylaxis in Patients with Predicted Severe Acute Pancreatitis (PROPATRIA), a multicenter, randomized, double-blind, placebo-controlled trial of 298 patients with predicted severe acute pancreatitis, found no significant difference in the risk of infectious complications in patients who received a multispecies probiotic preparation compared to placebo (relative risk 1.06, 95% CI 0.75 to 1.51).²⁵ Probiotic use, however, was associated with an increased risk of mortality (relative risk 2.53, 95% CI 1.22 to 5.25), which was attributed to deleterious effects on the small bowel.²⁵ This study contends that, at the least, probiotics should not be considered risk-free in critically ill patients, particularly in patients with predicted severe acute pancreatitis.

SAFETY AND REGULATION

Probiotics have been consumed by humans for thousands of years in food products such as fermented milk and alcoholic beverages. Due to this long history of consumption and exposure, probiotics are generally considered safe. In fact, the Food and Drug Administration (FDA) has classified several microorganisms including lactobacilli, *Bifidobacterium*, and yeast in the category of “generally regarded as safe” when used in food products.²⁸ Nevertheless, major areas of safety concern include the risk of sepsis and the potential for transfer of antibiotic resistance between probiotics and pathogenic bacteria. For example, there is a theoretical concern that *Lactobacillus* strains may transfer their vancomycin-resistant genes to pathogenic organisms such as enterococci and *Staphylococcus aureus*.¹¹ However, conjugation studies have found this transfer to be quite uncommon and may be attributed to the chromosomal location of *Lactobacillus*' vancomycin-resistant genes.^{11, 26, 27}

Although rare, reports of bacteremia and fungemia have been temporally related to probiotic use of *Lactobacillus* species, *Bacillus subtilis*, and *Saccharomyces boulardii*.^{11, 28} A review of the risks of probiotic use in clinical practice found that the majority of the cases responded to antibiotic therapy; however, some have resulted in septic shock and death.¹¹ Proposed major risk factors for probiotic sepsis include immune compromise and premature birth. Minor risk factors include central venous catheter, impaired intestinal epithelial barrier, jejunostomy administration of probiotics, concomitant use of broad spectrum antibiotics for which the probiotic is resistant, probiotics with properties of high mucosal adhesion, and cardiac valvular disease. It is suggested that the presence of a single major or more than one minor risk factor merits caution during probiotic use.¹¹ Many critically ill patients easily fulfill these requirements for caution.

In 1990, Finland introduced *L. rhamnosus GG* into dairy products. From 1990 to 2000, a period of increased probiotic use, the proportion of *Lactobacilli* bacteremia did not increase as assessed by blood cultures from Helsinki University Central Hospital and Finland's National Infectious Disease Register.²⁹ Although these results support the safety of probiotics, especially *Lactobacillus* strains, in healthy persons, they do not directly address the safety of probiotics use in the critically ill.

Probiotics are widely available in health-food stores in capsule, tablet, sachet, wafer, and liquid form. Under the Federal Food, Drug and Cosmetic Act, probiotics can be regulated as dietary supplements, foods, or drugs depending on the product's intended use.³⁰ If marketed as dietary supplements, probiotics are not subject to the same regulations regarding safety, purity, or potency as drugs are. If intended as a drug, probiotics must undergo review and approval by the FDA. However, most probiotics currently being studied are sold as foods or dietary supplements that do not generally meet the requirements of good manufacturing practices for drugs or biologics.³¹ The potential inconsistencies in composition of probiotics presents a challenge for clinical researchers investigating these products for new drug indications since data obtained from research on one strain do not necessarily extrapolate to other strains.³¹ Manufacturing processes that ensure the safety, dosing, purity, composition, and stability are imperative to ensure uniformity and replication of results.

CONCLUSION

Probiotics have been studied for use in a wide range of indications. They appear to be safe and effective in medically stable patients; however, the benefits in the critically ill have yet to be validated. Although several trials have shown possible benefits of probiotics in terms of enhancement of surrogate markers of immune function and reduction of bacterial colonization, demonstration of favorable clinical outcomes in randomized controlled trials with ICU patients is still necessary.^{23, 32} In fact, the safety of probiotics in critically ill patients remains controversial. Physiological changes during critical illness may adversely affect the safety of probiotics. Moreover, the effects of one probiotic strain in a particular patient population cannot be generalized to others. Therefore, additional large multicenter, randomized, controlled trials in adult critically ill patients are needed to determine the efficacy and safety of the various strains of probiotics in this patient population.

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P&T COMMITTEE BRIEF SUMMARY April 15, 2008

FORMULARY ADDITIONS	DOSAGE FORM(S), STRENGTH(S)	THERAPEUTIC CLASSIFICATION	USE	USUAL ADULT STARTING DOSE
Ranibizumab (Lucentis®)	Single-use glass vial provides 0.05 mL of 10 mg/mL solution for intravitreal injection.	Recombinant monoclonal antibody	Wet age-related macular degeneration	0.5 mg (0.05 mL) administered by intravitreal injection once a month (~28 days). Treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible.
Decitabine (Dacogen®)	Single-dose vial, containing 50 mg of decitabine	Hypomethylating agent	Treatment of myelodysplastic syndromes	The recommended Dacogen dose is 15 mg/m ² administered by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days.
Insulin detemir (Levemir®)	Each package size contains 100 Units of insulin detemir per mL (U-100): 10 mL vial 3 mL FlexPen®	Insulin analogue	Long-acting insulin used in patients with Type 2 diabetes	Individualized
Hyaluronic acid (Perlane®, Restylane®)	Single dose 1 mL disposable glass syringe	Hydrophilic gel	Correction of moderate to severe facial wrinkles and folds	Individualized

FORMULARY DELETIONS

Pegaptanib (Macugen®)

Replaced with ranibizumab (Lucentis®)