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NUTRITION AND OBESITY (SA MCCLAVE, SECTION EDITOR)

Bugs or Drugs: Are Probiotics Safe for Use in the Critically Ill?

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Abstract Probiotics are living microorganisms which have demonstrated many benefits in prevention, mitigation, and treatment of various disease states in critically ill populations. These diseases include antibiotic-associated diarrhea, *Clostridium difficile* diarrhea, ventilator-associated pneumonia, clearance of vancomycin-resistant enterococci from the GI tract, pancreatitis, liver transplant, major abdominal surgery, and trauma. However, their use has been severely limited due to a variety of factors including a general naïveté within the physician community, lack of regulation, and safety concerns. This article focuses on uses for probiotics in prevention and treatment, addresses current concerns regarding their use as well as proposing a protocol for safe use of probiotics in the critically ill patient.

Keywords Probiotics · Critical care · Indications · Safety · Review

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Introduction

Probiotics have been utilized for centuries and have a long history of safety in clinical. Many global healthcare organizations, including the World Health Organization, have attributed various health benefits to continued ingestion of probiotics [1–3]. Regulatory bodies define probiotics as living microorganisms which, when ingested in adequate amounts, provide health benefits to the host. [4]. The commensal relationship which we have with the bacteria that live on and within us has been known for decades. However, recent evidence has established that this host-microbe relationship is much more complex and intertwined than ever conceived.

The beneficial mechanisms of probiotics are numerous and include improved gastrointestinal barrier function, maintaining optimal pH and redox potential at the mucosal barrier, modification of the gut flora by inducing host cell antimicrobial peptides, release of antimicrobial factors, competing for epithelial adherence at binding sites on the mucosa, and immunomodulation to the advantage of the host. [5]. Prebiotics are ingestible agents that selectively promote the growth or activity of beneficial bacteria in the host. Synbiotics are a combination of prebiotics and probiotics designed to improve overall survival of the probiotic and promote colonization of the intestinal tract [4]. Commonly used organisms in probiotics include *Lactobacillus* species, *Bifidobacterium* species, *Escherichia coli*, *Streptococcus* species, and *Saccharomyces* [6].

Probiotics are very difficult to study given the multitude of confounding variables, heterogeneity of the ICU population, wide variety of available products, and nonstandardized dosing and treatment durations, leading to difficulty generalizing the results to a large population. They have shown benefit in critically ill patients with a variety of disease states, both prophylactically and as a treatment modality. Nonetheless,

these benefits are often overshadowed by the theoretical potential risks of probiotic use, including promotion of antimicrobial resistance, iatrogenic infection, as well as a general naiveté regarding dosing, indications, and which strains may provide the most benefit to the given patient. There is tremendous potential for benefit with probiotic therapy in the critically ill patient population, but due to the risks delineated, current use by most practitioners is limited. This review will focus on the rationale for and against the use of probiotics in critically ill patients, optimal delivery to the gastrointestinal tract, as well as proposing a protocol for widespread, safe use of probiotics in this unique patient population.

Prevention

Antibiotic-Associated Diarrhea

Antibiotic-associated diarrhea (AAD) is a prevalent consequence of antimicrobial use, especially in hospitalized and ICU patients due to the almost universal use of antimicrobial agents. AAD is the result of rapid alterations to the gut microbiota which cause an imbalance in the normal flora leading to diarrhea that usually occurs 2 to 8 weeks after antimicrobial exposure [7–9]. AAD occurs in approximately 5–30 % of critically ill patients; however, incidence varies based on the antimicrobial used and host factors [10]. Any antimicrobial can cause the microbiota changes and serve as the etiology of AAD, but the antibiotics most frequently implicated are clindamycin, cephalosporins, and aminopenicillins [6, 11]. Probiotics work to prevent AAD by reintroducing an intestinal flora which produces an environment conducive to reestablishment of the host normal flora, enhancing overall immune response by multiple mechanisms and clearing potential pathogens [10, 12]. The use of probiotics for the prevention of AAD has been well-described in the literature; unfortunately, most of these trials have been completed outside of the intensive care unit, which makes it difficult to extrapolate results to critically ill patients.

A recent meta-analysis conducted involving 82 randomized controlled trials found that probiotics, particularly *Lactobacillus*- and *Saccharomyces*-based products significantly reduced the incidence of AAD (RR 0.58, 95 % CI 0.5–0.68) with a number needed to treat (NNT) of 13 ($p<0.001$). Although this meta-analysis looked at trials involving mostly outpatients, the findings were similar in the subgroup analysis of hospitalized patients (RR 0.55, 95 % CI 0.42–0.72, NNT=10, $p<0.001$) [8]. A separate meta-analysis conducted looking at probiotics and the prevention of AAD involving 34 randomized controlled trials found similar results (RR 0.53, 95 % CI 0.44–0.63, NNT=9). It is important to note that both meta-analyses cited a significant heterogeneity amongst trials regarding dose, frequency, and product formulation which makes it difficult to determine an optimal probiotic regimen for this indication [13]. Caution should be taken with equating *Saccharomyces* with probiotics as it is not a true "probiotic" by strict definition and has been associated in case reports with fungemia in ICU patients [14].

Clostridium difficile-Associated Diarrhea

Probiotics have also proven efficacious in the prevention of a more severe form of AAD, *Clostridium difficile* (*C. difficile*). *C. difficile* is an anaerobic gram-positive, spore-forming bacterium that is the most lethal bacterial-induced diarrhea in the Western world. *C. difficile* has been shown to establish itself in the colon and proliferate in the setting of antibiotic-induced changes in the native flora. *C. difficile* bacterial overgrowth causes fluid secretion and extravasation, inflammation, and damage to the mucosal barrier which leads to a variable amount of diarrhea results, with pseudomembranous colitis, toxic megacolon, *C. difficile* sepsis, and death in the more severe cases if not aggressively managed [15]. Over 90 % of *C. difficile*-associated diarrhea (CDAD) occurs during or after antibiotic use, and approximately 30 % of cases will recur [16]. Probiotics work to decrease CDAD through improved immune function and minimizing intestinal colonization with *C. difficile* [6, 11, 17–19]. Several studies conducted in animals have demonstrated that *Saccharomyces boulardii* in particular combats *C. difficile* in a variety of ways including degrading toxins A and B, destroying the *C. difficile* colonic receptor, and increasing secretory IgA levels in the intestine [6, 20, 21].

The beneficial effects of probiotics for prevention of CDAD have been variable in relation to patient population and strains and doses of probiotics used, but findings have demonstrated an overall benefit in patients who are on concurrent antimicrobials [22]. A recent Cochrane review including 31 studies involving 4,492 patients was conducted to determine if probiotics prevented CDAD. Probiotics were found to decrease risk of CDAD by 64 % (RR=0.36, 95 % CI 0.26–0.51). The review found that the combination of *Lactobacillus acidophilus* and *Lactobacillus casei* was more efficacious in preventing CDAD when compared to *Lactobacillus rhamnosus* alone. Authors concluded that probiotics are safe and effective for the prevention of CDAD in patients who are not immunocompromised or severely debilitated [23•].

These findings were replicated in another meta-analysis involving 20 trials and 3,818 patients. Probiotics decreased the rate of CDAD by 66 % overall (RR=0.34, 95 % CI 0.24–0.49). This meta-analysis did not separate inpatients versus outpatients; however, 18 of the 20 trials included inpatients. Although this meta-analysis found no significant difference in efficacy between strains of probiotics, studies using multiple strains of probiotics at one time demonstrated an increased efficacy in preventing CDAD ($p=0.06$) [24]. Neither of these

two meta-analyses noted any increase in adverse effects due to probiotic administration [23•, 24]. It is important to emphasize that many of these effects are species specific. This was well illustrated by the recent large multicenter randomized control trial in nearly 3,000 patients at high risk for developing AAD and CDAD. Patients were given a combination of *L. acidophilus* and *Bifidobacterium bifidum*, and no benefit was noted [25••].

Vancomycin-Resistant Enterococci

Due to the efficacy of probiotics in preventing CDAD, it was postulated that a similar effect could be seen in prevention of vancomycin-resistant enterococci (VRE). Similar to *C. difficile*, VRE colonizes the intestine and can be transmitted to other patients, as well as transferring resistance genes to other bacteria. Probiotics are hypothesized to decrease overall intestinal colonization of VRE as well as improve the immune response within the intestine to VRE itself [26]. Unfortunately, there is limited data regarding the overall efficacy of probiotics in the prevention of VRE reinfection, colonization, and transmission. One randomized, placebo-controlled trial compared rates of VRE clearance in 27 renal patients who were swab positive for VRE given placebo or *L. rhamnosus* GG in a yogurt preparation. All patients given probiotics cleared VRE via fecal test and remained VRE free at 4 weeks compared with just one patient in the placebo group (8.3 %). Eight patients from the placebo group crossed over to the probiotic group, and all remained VRE free at 4 weeks [27]. Another randomized, placebo-controlled trial looking at probiotics and intestinal colonization of VRE involved nine patients given *L. rhamnosus* Lcr35 or placebo. There was no difference seen in clearance of VRE between the two groups at week 11, although six of the nine patients did clear VRE during the trial, including four patients on probiotics [26].

Ventilator-Associated Pneumonia

Probiotics have also demonstrated preventative benefits in ventilator-associated pneumonia (VAP). VAP usually occurs within 48 to 72 h of intubation and has been noted to affect 15 to 30 % of mechanically ventilated patients. VAP not only leads to increased length of stay but also an increase in morbidity, mortality, and overall hospital costs [28–34]. The effects of probiotics in the prevention of VAP have yet to be fully proven but have been postulated to include decreased bacterial translocation, improvement in gut-mucosal barrier, decreased biofilm production on the endotracheal tube, and immunomodulation [35–37].

Morrow et al. conducted a randomized controlled trial involving 138 patients at high risk for VAP. Patients were randomized to placebo or two capsules of 10^9 colony-forming units of *L. rhamnosus* GG twice daily. One capsule was administered via swabbing the oropharynx; the other was given enterally. Patients randomized to probiotics not only experienced fewer VAP infections (40 vs. 19.1 %, $p=0.007$) but also received antimicrobials for a shorter duration (8.6± 10.3 vs. 5.6±7.8 days, $p=0.05$). This study found no increase in adverse effects in patients on probiotics as compared to those on placebo. Authors concluded that probiotics could be used to decrease rates of VAP in a high-risk, critically ill population without increasing the incidence of adverse effects [38].

The benefits of probiotics in the prevention of VAP have also been demonstrated by multiple meta-analyses. A literature review conducted by Schultz et al. showed a decrease in VAP incidence when probiotics were administered in three out of eight trials. The authors noted that this decrease in VAP was not associated with any increase in adverse events related to administration of probiotics [37]. These findings were replicated in a meta-analysis conducted by Siempos et al. involving five trials and 795 patients, which found that probiotics significantly decreased VAP rates (OR=0.61, 95 % CI 0.41–0.91). These findings were similar despite route of administration or product used. However, the decreased incidence of VAP was not associated with a difference in mortality amongst the groups [39]. Finally, a meta-analysis conducted by Petrof et al. investigating the overall efficacy of probiotics in critically ill patients found a significant reduction in VAP rates when probiotics were administered (RR=0.75, 95 % CI 0.59–0.97, $p=0.03$) [40••].

Treatment

Clostridium difficile-Associated Diarrhea

In addition to showing benefit in prevention of high-risk infections, probiotics have also demonstrated efficacy in the treatment of common disease states in the critically ill population. As described previously, probiotics have shown efficacy in the prevention of CDAD, but they have also shown benefit in the treatment of established CDAD. Probiotics are postulated to work in a similar method for both prevention and treatment of CDAD by improving overall immune function, decreasing production of toxins, and restoring normal colonization [41].

One randomized controlled trial examined the efficacy of *S. boulardii* for the treatment of recurrent CDAD when combined with oral vancomycin or metronidazole. Use of *S. boulardii* resulted in a decreased relative risk of CDAD recurrence when compared with placebo for all patients (RR 0.43, 95 % CI 0.20 to 0.97) [42]. These findings were duplicated in another trial which looked at the efficacy of *S. boulardii* when combined with high-dose (2 g/day) oral vancomycin compared with placebo for recurrent CDAD. The

addition of *S. boulardii* decreased the overall rate of recurrences (16.7 vs. 50 %, $p=0.05$) when compared with placebo with no increase in significant adverse reactions. Unfortunately, these results were not duplicated in patients on low-dose (500 mg/day) oral vancomycin or metronidazole leading the authors to conclude that *S. boulardii* may be most beneficial in patients with severe, recurrent CDAD [43].

A Cochrane review including four studies examined the overall efficacy of probiotics in the treatment of recurrent CDAD when combined with either vancomycin or metronidazole. Three of the included studies found no benefit when probiotics were administered compared to placebo. Thus, the authors concluded that more data was necessary to recommend probiotics as adjunctive agents in the treatment of CDAD [41]. Probiotics are not currently recommended as monotherapy in the treatment of CDAD but have clearly demonstrated efficacy as adjunctive therapy in patients with recurrent CDAD, especially when *S. boulardii* is administered.

Acute Pancreatitis

Probiotics have also demonstrated efficacy in the treatment of acute pancreatitis, although use is still controversial. The proposed benefit of probiotics in pancreatitis is a reduction in bacterial translocation from the small intestine to the pancreas which can help to reduce bacterial complications associated with pancreatitis [6, 44]. Multiple trials and case series in both animals and humans have demonstrated the benefit of a variety of strains of probiotics and synbiotics in acute pancreatitis, including reducing the overall incidence of intestinal bacterial translocation, infected pancreatic necrosis, and the need for surgical intervention [45–54]. A recent study conducted by Wang et al. looked at the effects of the addition of ecoimmunonutrition (live *Bacillus subtilis* and *Enterococcus faecium* cultures) to enteral nutrition in patients with acute pancreatitis. The addition of ecoimmunonutrition decreased the overall rate of pancreatitic sepsis and multiorgan dysfunction syndrome (MODS) over enteral nutrition alone ($p<0.05$ for both), and a nonsignificant decrease in mortality was also noted [55].

Despite these studies reporting the benefit of probiotics in pancreatitis, the PROPATRIA trial demonstrated major safety issues regarding the use of probiotics in acute pancreatitis. The authors found that their multispecies probiotic formulation led to an increase in bowel ischemia and an increased mortality (RR 2.53, 95 % CI 1.22–5.25) without a decrease in infectious complications [56]. This result was thought to be multifactorial; patients in the probiotic group had a higher incidence of organ failure and transmural necrosis of the bowel near the site of probiotic delivery into the bowel. The probiotics were administered via small bowel feeding tube combined with soluble and insoluble fibers. It was felt that local fermentation of the soluble fibers by the bacteria in the relatively immobile small bowel was a major risk factor for adverse effects localized acidosis and bowel wall injury. Shortly after this trial was published, an independent review was conducted that found significant issues with the design and conduct of the trial, including dosing and administration of probiotics [54, 57]. Due to this criticism, the authors are currently repeating this trial with no changes in the overall protocol, but with changes to the conduct of the trial.

Liver Transplantation

Bacterial translocation also plays a crucial role in infection rates as well as outcomes for liver transplantation patients. These patients undergo extensive surgeries for the transplant itself and are immunosuppressed, and most patients are malnourished due to the chronic liver disease. All of these factors combine to increase the risk of infection as well as overall morbidity and mortality. *Lactobacillus* species in particular have demonstrated benefit in this population by initiating immunoglobulin production, decreasing inflammatory cytokine release, and decreasing permeability of the intestines [58, 59].

Two separate clinical trials have demonstrated benefits of probiotics on infection rates in patients post liver transplant. The first trial looked at three groups: living *Lactobacillus plantarum* 299 plus a fiber-containing enteral formula, heat-killed *L. plantarum* 299 plus a fiber-containing enteral formula, or standard enteral nutrition formula. Patients given the living probiotics and fiber had significantly decreased rates of infection compared with patients on both the standard formula and heat-killed probiotics plus fiber (13 vs. 48 vs. 34 %, respectively, $p=0.017$). Patients on living probiotics also had a decreased duration of antimicrobial therapy, and mean total hospital and ICU stay, although these findings were not statistically significant [60]. The second trial investigated the administration of four strains of *Lactobacillus* and enteral nutrition with four fibers compared with enteral nutrition with fibers alone in patients post liver transplant. Patients given probiotics had a decreased incidence of bacterial infection compared with those given enteral nutrition alone (3 vs. 48 %, $p<0.05$), as well as decreased duration of antimicrobial therapy (0.1 vs. 3.8 days, $p<0.05$) and a nonstatistically significant decrease in ICU length of stay [59].

Major Abdominal Surgery

Patients are also at high risk for infectious complications after major abdominal surgeries. As in liver transplantation, these patients are often malnourished, immunocompromised, and at high risk for intestinal bacteria translocation. The benefits of probiotics are similar to those seen post liver transplant, including immune regulation, preventing bacterial overgrowth

in the intestines, and preserving the mucosal gastrointestinal barrier function [61–64]. Multiple trials involving different probiotic formulations both with and without enteral nutrition have been conducted; most have demonstrated a decreased overall rate of infection, as well as a decreased duration of antimicrobial therapy [58, 65]. One trial found no difference between probiotics and placebo in relation to bacterial translocation and infection rates; however, the probiotic dose used was lower relative to doses used in other trials, which may have affected results [66].

A meta-analysis was conducted by Pitsouni et al. to determine the overall efficacy of probiotics in major abdominal surgery. Nine randomized controlled trials involving 733 patients were included for review with all trials utilizing varying probiotic formulations. Overall, patients who were given probiotics had a decreased duration of antimicrobial therapy (OR −4.01, 95 % CI −5.11 to −2.92), decreased hospital length of stay (OR −2.7, 95 % CI −5.15 to −0.25), and decreased incidence of infection (OR 0.26, 95 % CI 0.12 to 0.55) [63].

Trauma

Trauma patients have also demonstrated potential benefits from probiotic therapy due to similar mechanisms seen in postoperative liver transplantation and abdominal surgery [67, 68]. A randomized controlled trial investigated the effects of a synbiotic formulation with four strains of probiotics versus placebo to determine if the benefits seen in major abdominal surgery and liver transplantation would translate to critically ill trauma patients given the similar acute phase inflammatory response. Patients given synbiotics had a decreased rate of infection (63 vs. 90 %, p=0.01), severe sepsis (49 vs. 77 %, p=0.02), mean days in the ICU (27.7 vs. 41.3 days, p=0.01), and mean days on mechanical ventilation (16.7 vs. 29.7 days, p=0.001) as compared to placebo [68].

A second randomized controlled trial conducted in a trauma population confirmed these results. Patients on synbiotics with four strains of probiotics had decreased intestinal permeability, which was not seen in patients on fiber-enhanced enteral nutrition, immunonutrition, or peptide enteral nutrition. Patients given synbiotic also had decreased rates of pneumonia (p=0.03) as well as overall infection (p=0.003), which may have been due, in part, to decreased intestinal permeability [67].

Risks of Probiotic Use in Critically Ill Patients

Despite the wide variety of disease states in which positive effects of probiotics have been noted in both prevention and treatment in the critically ill, there are still many questions regarding overall safety, dosing, and administration. Probiotics are considered to be food supplements by the Food and Drug Administration (FDA) and thus are not regulated as other medications administered in the critical care setting. There are no manufacturing standards for dosage and preparation which may lead to variations in efficacy and potential side effects, even among identical strains of probiotics [1, 69, 70•]. Despite these variations, probiotics have been classified as "generally regarded as safe" (GRAS) by the World Health Organization and the FDA [2, 71] Two noteworthy reservations regarding the use of probiotics in the hospital setting are the incidence of adverse effects such as systemic infections and the transfer of antimicrobial resistance genes from the probiotics to gastrointestinal flora and other pathogenic bacteria [1, 2].

The incidence of secondary infections and abscesses is a concern many practitioners have voiced regarding the use of probiotics in critically ill patients. This risk can be found both in patients receiving probiotics as well as neighboring patients and potentially health-care workers responsible for probiotic administration. To date, there have been no reports of bacteremia or fungemia associated with probiotic administration in otherwise healthy patients. Additionally, bacteremia and fungemia have not been reported as adverse effects in clinical trials involving probiotics despite a vast array of patient populations studied, including many high-risk groups [1]. Case reports have found multiple risk factors for probiotic-related sepsis including: immunosuppression, prosthetic heart valves, impaired intestinal function, presence of a central venous catheter, administration of probiotic by jejunostomy, concomitant administration of broad-spectrum antimicrobials to which the probiotic is resistant, and poorly controlled diabetes mellitus [1, 10].

In a case series including all reports of *Lactobacillus*-related bacteremia from 1950 to 2003, there were 129 cases of probiotic-related bacteremia, 73 cases of endocarditis, and 39 cases of localized infection, including peritonitis, abscesses, and meningitis. Of the 129 patients with bacteremia, 104 patients had underlying immunosuppression due to cancer, transplantation, diabetes mellitus, or use of broad-spectrum antimicrobials. *L. casei*, *L. plantarum*, and *L. rhamnosus* were the most common strains to cause bacteremia or endocarditis, but they are also among the most commonly used strains of probiotics [72].

Saccharomyces strains of probiotics have also been associated with systemic infections. A literature review found 92 case reports of *Saccharomyces* infections between 1950 and 2005, with 72 of those infections being bacteremia. The two most common strains that caused infection were *S. boulardii* and *Saccharomyces cerevisiae*. Patients infected with *S. boulardii* had a better prognosis overall, but were less likely to be immunocompromised. The most common infection-associated variables included intravascular catheters and concomitant antimicrobial administration [73]. Despite these

reports, a study commissioned by the Agency for Healthcare Research and Quality confirmed the overall safety of probiotics in relation to incidence of bacteremia without mention of the limited safety data currently available [70•].

Another concern with probiotic administration is the spread of antimicrobial resistance genes from probiotics to other bacteria, including the normal gastrointestinal flora and pathogenic species present in the intestine [31, 74]. Probiotics have unique susceptibility patterns that vary based on species and strain, including some resistance to more commonly used broad-spectrum antimicrobials. Unlike other bacteria, probiotics typically do not house resistance genes on plasmids making it difficult for the gene to be readily transferable to other species. For example, many strains of *Lactobacillus* carry vancomycin and aminoglycoside resistance genes; however, these genes are chromosomal making them difficult to transfer to other bacterial species. In fact, there have been no studies showing *Lactobacillus* vancomycin or aminoglycoside resistance genes conjugated in other strains of bacteria [1, 75]. While antimicrobial resistance remains a valid concern, probiotics have yet to demonstrate a contribution to this ongoing problem [75].

Alteration or destruction of the normal flora of the intestine is yet another concern that has arisen with the use of probiotics. The normal flora of the intestine is vital to many metabolic activities, and changes to the flora could potentially alter these metabolic activities, leading to adverse effects. However, this process has yet to be demonstrated by any study to date [1]. There is a potential risk of probiotics leading to deconjugation of bile salts, in turn increasing the risk of colon cancer. However, there is no data to support this theory, and in contrast, animal data supports that probiotics could have promise in preventing colon cancer [2]. Finally, due to the fact that a large component of the immune system is present in the intestinal tract and immune modulation is a cited benefit of probiotics, there are thoughts that subsequent immunosuppression could occur, especially in pregnancy, neonates, and children. Once again, multiple clinical trials have been unable to confirm these adverse effects and instead have demonstrated no adverse immunologic alterations [1, 2].

Studies in infants and adults have demonstrated that probiotics can influence the composition of intestinal flora in healthy patients. The changes to intestinal flora have not demonstrated any adverse effects in healthy patients. Because probiotics antagonize pathogens and protect the intestinal mucosa against colonization of pathogenic bacteria, these effects are likely beneficial. It has also been demonstrated that probiotics aid in proliferation of normal intestinal flora which is extremely beneficial to patients who have experienced a depletion of normal flora secondary to antimicrobial use [1].

Many argue that these safety issues exist not only for the patient receiving probiotics but also for neighboring patients given both the close contact and the number of patients that health-care workers interact with on a regular basis. Hennequin et al. demonstrated detection of bacterial strains 1 m away from the site of the probiotic being opened for nasogastric administration. These strains persisted on room surfaces for 2 h. Additionally, authors found the probiotic strains on the hands of health-care workers despite vigorous hand washing [14, 76]. Given these findings, transfer of a probiotic from one patient to another is feasible, which introduces an infection risk, especially if patients have risk factors for probiotic-related sepsis. Caution should be taken when administering probiotics for the safety of all patients. A safe protocol for administration will be further addressed in the upcoming sections of this article.

Despite vast amounts of data regarding the use and safety of probiotics, multiple barriers remain that prevent routine use of these products in a critical care setting. A lack of societal guidelines regarding the use of these products leaves health-care practitioners with more questions than answers regarding patient populations, dosages, and duration of therapy. In addition, there is a lack of available probiotic protocols to model product selection, dosing, and delivery. The less stringent regulation of probiotics relative to other treatment modalities leaves many unanswered questions regarding which strains of probiotics should be utilized and the safety between products. Varying beliefs and attitudes regarding efficacy and safety of probiotics due to previous experience, a lack of knowledge of current literature, or just an overall naïveté regarding the indications for probiotics have led to hesitance in routine use in the ICU. Due to all of these factors, resistance from leadership, from within departments, and amongst health-care providers has prevented adoption of regular use of probiotics. These human factors significantly contribute to erratic implementation of new products or treatment algorithms and have severely limited use of probiotics in the hospital and critical care setting.

Ideal Protocol for Widespread Use of Probiotics: Lessons Learned from Randomized Controlled Trials

Despite the vast array of data regarding use of probiotics, many questions remain, most relating to optimal administration and product selection. Randomized controlled trials conducted using a variety of formulations and administration methods have provided insight for optimal delivery. Although the benefits of probiotics have been demonstrated in multiple disease states, institution-specific protocols are crucial to minimizing adverse effects [69]. Outlined below is an evidence-based proposal for a protocol to optimize probiotic use in the critically ill. This protocol is based on synthesis of current data and is adaptable to a variety of clinical situations.

Patient Selection

Use of probiotics in the critically ill should be limited to that patient with an indicated disease state and no relative contraindication. Probiotics should be considered for use in those patients who have had liver transplantation, major abdominal surgery, or trauma, patients with pancreatitis or CDAD, patients requiring broad-spectrum antimicrobial therapy, or those patients requiring mechanical ventilation. There is limited data regarding prevention of VRE infection, but in high-risk patients without relative contraindications, probiotics could be considered. Due to an increased risk of adverse effects from probiotic administration, relative contraindications to probiotic use include immunosuppression, central venous catheterization, and cardiac valvular disease (only for *Lactobacillus* species) [1, 10].

Timing

Timing of probiotic therapy in relation to onset of illness is also controversial. For disease states discussed previously, studies have shown benefit when probiotics are initiated shortly after the onset of the disease. When being used preventatively, benefits are seen with probiotic initiation upon the introduction of a risk factor for the disease state, such as the initiation of antibiotics or introduction of mechanical ventilation [38, 40••]. There is currently no data regarding delayed probiotic therapy or utilizing these products as salvage therapy. Therefore, when probiotics are indicated, they should be initiated as soon as possible.

Type of Preparation

Commercially prepared formulations of probiotics are recommended as it is easier to discern ingredients included in the preparation and most clinical trials have utilized these products. There is limited data regarding the use of "homemade" probiotic preparations. The strain of probiotic utilized should be institution specific. However, probiotics containing *L. plantarum*, *L. acidophilus*, and/or *L. rhamnosus* should be used preferentially due to larger amounts of data available with these strains [77•]. A list of commonly used commercially prepared probiotics has been included in this review (Table 1) along with dosing and administration information [78–80].

Choice of probiotic preparation is also influenced by the number of strains within the product. In a meta-analysis of 23 trials looking at the effects of probiotics in the critically ill, significant benefits were noted, but no trial included more than eight strains of probiotics. Thus, administration of greater than eight strains is likely unnecessary. Nine of the included trials administered a single strain of probiotic demonstrating similar efficacy to those trials using multiple strains [40••].

Randomized controlled trials have also investigated the optimal preparation of probiotics. Probiotics have been formulated as pills, capsules, packets, yogurt, and oatmeal preparations. There is no data supporting one method over another; however, there are problems that arise with administration of the various formulations [40••, 69]. Pills, capsules, and packets lead to ease of administration in patients able to take oral medications; however, these formulations present a problem in patients with a nasogastric tube requiring enteral nutrition. Yogurt preparations can also be easily administered to patients with oral intake but present problems for patients on

Table 1 Commonly available probiotic products [78–80]

Probiotic	Preparations	Delivery methods	Dosing
Bifidobacterium sp.	Yogurt (Activia®)	Oral/enteral	4–8 oz daily
	Capsule (Align®)		1 capsule daily
Lactobacillus acidophilus	Capsule	Oral/enteral	1–2 capsules daily
	Powder (Superdophilus®, Megadophilus®)		1–4 packets daily
	Tablet (Kala®)		1–2 tablets daily
Lactobacillus rhamnosus GG	Capsule (Culturelle®)	Oral/enteral Oropharyngeal swabbing	1 capsule daily to twice daily
Lactobacillus combination products	Granules (Floranex™, Lactinex™) Powder	Oral/enteral	1 packet 3–4 times daily
	Chewable Tablet (Floranex™, Lactinex™) Wafer		4 tablets 3–4 times daily
Saccharomyces boulardii	Capsule (Florastor®) Powder (Florastor Kids®)	Oral/enteral	250 mg twice daily
Combination *Lactobacillus* sp., *Bifidobacterium* sp., *Streptococcus thermophiles*	Powder (VSL#3®)	Oral/enteral	1–8 sachets daily
	Capsule (VSL#3®)		2–32 capsules daily

tube feeds, patients who are lactose intolerant, and patients who are otherwise nil per os (NPO). Mixing these preparations with water allows for easier enteral administration. Pill preparations are preferred in most patient populations.

Dose and Duration of Therapy

The Petrof meta-analysis also demonstrated similar rates of infectious complications despite the concentration of the product administered ($\geq 5\times10^9$ or $<5\times10^9$ colony-forming units (CFU)/day) [40••]. McNaught et al. found a decreased overall efficacy with doses $<5\times10^7$ CFU/day. Therefore, higher doses should be utilized to maximize the benefit without concern for an increase in adverse effects [66].

Investigations have also targeted the question of whether swabbing the oral cavity with probiotics leads to similar benefits as administration via nasoenteric tube. Most clinical trials have utilized the enteral route for administration, as most benefits stem from colonization of the intestine [40••]. However, Morrow et al. trialed probiotic administration via the oropharynx in addition to the enteral route for prevention of VAP. This combined route of administration led to a decreased incidence of VAP and also fewer antimicrobial days compared to those given placebo [38]. This was the second study to demonstrate a decreased incidence of VAP with delivery of probiotics to the oropharynx [35]. Although enteral administration is preferred, these studies suggest patients on mechanical ventilation may benefit from oropharyngeal administration of probiotics as well.

Duration of probiotic therapy varies based on indication. When being utilized for prevention of VAP, AAD, and CDAD, probiotics should be continued until the risk factor is removed. Treatment regimens for probiotics should be continued for 14–21 days in the majority of patients, as that is the median treatment duration used in clinical trials.

Handling and Preparation of Probiotics

Regardless of the formulation, hand hygiene is imperative for health-care workers handling the probiotic preparation. Health-care providers should wear gloves when handling, preparing, and administering probiotic preparations. Gloves should be promptly discarded after use and followed by a thorough washing of hands. This practice minimizes exposure of other patients, visitors, and health-care workers to the probiotics. Additionally, health-care workers should be aware of and avoid any central lines including central venous catheters, peripherally inserted central catheters, and ports while administering probiotics. Opening of probiotic capsules should be done away from patients in a confined space, preferably in the pharmacy, to avoid aerosolization of spores and contamination of sterile sites. If capsules or tablets are being utilized in patients receiving enteral medications, they should be compounded into a suspension in the pharmacy prior to dispensing. Restriction from certain units should also be considered, including units with a high ratio of immunosuppressed patients as the risk of infection may outweigh the benefits of the probiotic. *S. boulardii* carries an increased risk for environmental contamination, warranting extra caution when handling the product [69].

Conclusion

Probiotics have shown benefits both in the prevention and treatment of multiple disease states; however, these agents need to be handled carefully. The technology is now available for high-quality studies that will elucidate the changes observed and the potential outcome benefits from replacing healthy flora. Such studies should allow the clinician to capitalize on the beneficial influences of the microbiome while attenuating the detrimental effects. Risks and benefits should be considered in every patient as not every critically ill patient is an appropriate candidate for probiotic therapy. A protocol for use can help to maximize benefit and minimize adverse effects. Protocols should be based on current institution-specific policies and patient care procedures, culture, and the elected formulary probiotic preparation. However, many barriers remain to the implementation of these protocols, including safety concerns and a general lack of knowledge regarding product selection, dosing, administration, and overall efficacy. Once these barriers are overcome, an effective protocol can lead to optimal use of these “bugs” in the critically ill population.

Compliance with Ethics Guidelines

Conflict of Interest Lindsay M. Urben, Jennifer Wiedmar, Erica Boettcher, Rodrigo Cavallazzi, and Robert G. Martindale have nothing to disclose.

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- • Of importance
- •• Of major importance

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