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REVIEW ARTICLE

The Role of Probiotics in Critically Ill Adult Patients with Pneumonia

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Introduction

There is increased interest in the role of the gastrointestinal (GI) or gut microbiome and its role in prevention and treatment of disease. The gut microbiome alone consists of approximately 400 strains of bacteria, fungi, and parasites. Anaerobes are the predominant type of microorganism in the GI tract with *Firmicutes* and *Bacteroidetes* being the dominant phyla [1-4]. The gut microbiome is involved in metabolism, host protection, and immune function. It plays an important role in metabolism of nondigestible carbohydrates such as polysaccharides enabling it to be absorbed and used for energy by the host. The microbiome can also produce vitamins and synthesize essential and nonessential amino acids [1]. In addition, the gut microbiome prevents pathogenic bacteria from thriving in the GI tract through multiple mechanisms. The microbiome competes for binding sites on the intestinal epithelial cells preventing the pathogen from attaching and entering the host cell. The microbiome also competes for nutrients in the GI tract enabling it to preserve its habitat and preventing the pathogenic bacteria from flourishing. In addition to competing for attachment sites and nutrients, the gut microbiome protects the host by producing bacteriocins which has an antimicrobial effect and inhibits the growth of pathogenic bacteria [5-8]. The gut microbiome also influences host immune function. A comparative study of six probiotic strains within the lactobacilli and bifidobacteria genera and showed equipotent T-cell and natural killer (NK) cell activation. There was a difference in cytokine activation between the two genera: The lactobacillus strains activated T helper 1 cytokines whereas the bifidobacterial strains had an anti-inflammatory effect [9]. There is also bidirectional communication between the gut and the brain referred to as the *gut-brain axis*. This means the gut microbiome is not limited to exhibiting local action but also has the ability to influence brain function and vice versa. Factors such as stress and inflammation increase intestinal permeability increasing the chance for bacterial translocation [4]. Probiotic use may also improve mood in patients suffering from depression. A meta-analysis of ten studies showed a significant improvement in mood (SMD = -0.684, 95% CI -1.296 to -0.0712, p = 0.029) in subjects with mild to moderate depression [10]. It is important to note that not all probiotic strains are shown to prevent or treat all illnesses. A systematic review and meta-analysis of 228 trials showed there was evidence to indicate strain and disease specific activity in the efficacy of probiotic strains. A limitation to this study is that it mostly included GI illnesses such as antibiotic induced diarrhea, irritable bowel syndrome, and *Helicobacter pylori* infection in its analysis. *L. rhamnosus* GG was identified as having disease specific activity towards nosocomial infections defined as having at least two randomized controlled trials (RTC) with significant efficacy [11]. Due to the gut microbiome's many modes of action, researchers are investigating the role of probiotics in the prevention and treatment of various conditions, including pneumonia in critically ill patients. This review provides a summary of available evidence on the use of probiotics for pneumonia in critically ill adult patients.

Epidemiology and pathophysiology

Lactobacillus, *Bifidobacterium*, *Escherichia*, *Strep-*

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tococcus, and *Saccharomyces* are the most commonly used genera in commercially available probiotic supplements [5-12]. According to the National Center for Complementary and Integrative Health, pro and prebiotics are the third most commonly used natural product used by 3.9 million Americans. Probiotic use has increased by 4-fold from 2007 to 2012 [13]. A study investigating the extent of probiotic use in hospitals found that 96% of the 145 hospitals included in the study used probiotics in 2.6% of hospitalizations. Probiotic use in hospitals increased 2.9-fold from 2006 to 2012 [14].

Mechanism in critically ill

Probiotics have several potential mechanisms in critically ill patients. They may improve the gut mucosal barrier function, decrease bacterial translocation and overgrowth of pathogenic microorganisms, antioxidative effects, suppressed immune cell proliferation, inhibited activation of nuclear factor kappa B, and immune function modulation. Critically ill patients experience several changes to gut microflora due to stress hormones, bacterial translocation, immunosuppression, ischemia of the gut, and receiving antibiotics. Probiotics may minimize colonization in the upper digestive tract, improve gut mucosal barrier function, decrease intestinal hyperpermeability, upregulate immune function, and reduce bacterial translocation which may reduce the risk of ventilator-associated pneumonia (VAP) in the critically ill [15,16].

Methodology

Relevant articles were identified using Medline with Full Text and the search terms “probiotic” and “critically ill patients or intensive care unit patients or critical care patients” and “pneumonia”. Search results showed 33 articles published on this topic. The filter function was used to only include articles in English. Using this filter reduced the article count to 32. Of the 32 articles, 6 were randomized controlled trials that had adult subjects and 2 were mata-analyses. All 8 were included in this review. Studies on pediatric patients were excluded as this review focused on adult patients.

Review of Literature

Several randomized controlled trials on the use of probiotics for pneumonia in critically ill patients have been published (Table 1). Studies involving probiotics for pneumonia in adult critically ill patients vary in pa-

Table 1: Evidence summary of probiotic use in critically ill adult patients with pneumonia.

Study	# of subjects	Study design	Strain of probiotic used	Patient population	Results
Zeng, et al. [17]	235	Prospective, open-label, randomized, controlled, multicenter	*Bacillus subtilis* 4.5 × 10^9/0.25 g and *Enterococcus faecalis* 0.5 × 10^9/0.25 g.	Medical, surgical, trauma, and neurologic critical care patients expected to be on mechanical ventilation for 48 hours or longer	• 43 patients in the probiotic group vs. 59 in control diagnosed with microbiologically confirmed VAP (36.4% vs. 50.4%; p = 0.031) • No significant difference in clinically diagnosed VAP between groups (40.7% vs. 53%; p = 0.059) • Patients who received probiotics had a greater probability of not developing VAP (p = 0.004) • The use of probiotics resulted in a reduction of 0.28 in risk ratio for VAP (95% CI 0.03-0.47) with number needed to treat of 7 patients to prevent one case of VAP • Patients in the probiotic group experienced longer time to onset of VAP (10.4 vs. 7.5 days; p = 0.022) • No significant difference between the probiotic and control groups in eradication of PPMO colonization (46.9% vs. 32.1%; p = 0.245) or acquisition of PPMO colonization (44.2% vs. 52.8%; p = 0.254) • Probiotics did not affect the gastric colonization of PPMOs (27.8% vs. 19.2%; p = 0.756) • No significant difference in duration of mechanical ventilation, duration of antibiotics for VAP, number of antibiotic-free days, days in the ICU, days in the hospital after ICU admission, ICU mortality, or in-hospital mortality • No adverse events reported with probiotic use

Barraud, et al. [18]	167	Double-blind, randomized, placebo controlled	2×10^{10} *Lactobacillus rhamnosus GG, Lactobacillus casei, Lactobacillus acidophilus*, and *Bifidobacterium bifidum*).	Mechanically ventilated patients in a medical ICU expected to be intubated for at least 2 days	• No significant difference in 28-day mortality (25.3% probiotic vs. 23.7% placebo; p = 0.80) or mortality at 90 days (31% vs. 30%; p = 0.90) • Probiotics did not affect ICU or hospital length of stay or organ failure reversal. • Decreased incidence of catheter-related bloodstream infections in the probiotic group (1.84 vs. 6.78 catheter-days; p = 0.005) • Less patients with catheter-related bloodstream infections in the probiotic group (3.4% vs. 13.7%; p = 0.005) • No difference in urinary tract infections, VAP, or combined ICU-acquired infections • Probiotic use did not affect colonization with multi-drug resistant bacteria • Subgroup analysis: reduction in 28-day mortality in patients with severe sepsis who received probiotics (odds ratio 0.38; 95% CI 0.16-0.93; p = 0.035) • No adverse effects were observed
Morrow, et al. [19]	146	Prospective, randomized, double-blind, placebo controlled	*Lactobacillus rhamnosus* GG	Mechanically ventilated patients at high risk for developing VAP	• Less VAP in probiotic group (19.1% vs. 40%; p = 0.007) • Patients who received probiotics received less days of antibiotics for VAP (5.6 vs. 8.6; p = 0.05) and *Clostridium difficile* associated diarrhea (0.5 vs. 2.1; p = 0.02) • Less *Clostridium difficile* associated diarrhea in probiotic group (5.8% vs. 18.6%; p = 0.02) • Similar duration of diarrhea between groups • No significant differences in mortality, duration of mechanical ventilation, hospital and ICU length of stay, or hospital charges between the two groups
Knight, et al. [20]	259	Prospective, randomized, placebo controlled	Synbiotic 2000 FORTE: *Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei* (10^{10} bacteria per sachet) and betaglucan, inulin, pectin, and resistant starch (prebiotics)	Enterally fed patients requiring mechanical ventilation for 48 hours or more	• VAP incidence similar in the synbiotic and placebo groups (9% vs. 13%; p = 0.42) • No significant differences in ventilator days, VAP episodes/1000 ventilator days, length of ICU stay, ICU or hospital mortality were observed between groups • The use of synbiotics did not affect the microbial species or colonization rates of potential pathogens • No adverse effects were reported

Forestier, et al. [21]	208	Prospective, randomized, double blind, placebo-controlled	*Lactobacillus casei rhamnosus*	Patients 18 years or older with an ICU stay longer than 48 hours and a nasogastric feeding tube	• Six patients in the placebo group acquired gastric *P. aeruginosa* (3 ceftazidime-resistant isolates). • Three patients in the probiotic group acquired gastric *P. aeruginosa* (1 ceftazidime-resistant isolate). • No statistically significant differences between the two arms in the delay in gastric acquisition of *P. aeruginosa.* • Thirteen positive samples of *P. aeruginosa* was detected in respiratory tract specimens (5 ceftazidime-resistant isolates) of subjects in the placebo arm. • Five positive samples of *P. aeruginosa* was detected in respiratory tract specimens (all ceftazidime-sensitive) of subjects in the probiotic arm. • A statistically significant difference between two arms was seen in acquisition delay of *P. aeruginosa* in the respiratory tract ($p < 0.05$). • *P. aeruginosa* caused VAP in 8 patients in the placebo arm and 3 patients in the probiotic arm (no statistically significant difference). • Seventeen patients in placebo arm and 6 patients in the probiotic arm either had gastric or respiratory tract *P. aeruginosa* growth ($p = 0.02$).
Shinotsuka, et al. [22]	49	Prospective, controlled, randomized, open-labeled	Probiotic: *Lactobacillus johnsonii La1* Prebiotic: Soybean polysaccharide	Patients on mechanical ventilation admitted to the ICU	• The proportion of enterobacteria growth in the tracheal secretion of subjects in the pre- and probiotic groups was not statistically significant. • There was non-significant decrease in bacterial isolation and increase in negative samples of gastric secretions on the 7th day in the pre, pro, and symbiotic groups compared to placebo. • There was no statistically significant difference between study groups in rates of nosocomial infections and VAP.
Klarin, et al. [23]	50	Prospective, randomized, active-controlled	*Lactobacillus plantarum 299*	Critically ill patients 18 years or older with an anticipated need for mechanical ventilation for at least 24 hours	• Eight patients in the probiotic arm and 13 patients in the chlorhexidine arm grew pathogenic bacteria in their oropharyngeal samples ($p = 0.13$)

tient populations, definitions of VAP, strains and doses of probiotics, study design, and sample size. A study published in 2016 by Zeng, et al. [17] is a prospective, open-label, randomized, controlled, multicenter trial evaluating probiotics in the prevention of VAP in critically ill patients. Two hundred thirty-five adult critically ill patients who were expected to be on mechanical ventilation for 48 hours or longer were included. This study included medical, surgical, trauma, and neurologic critical care patients. Patients excluded were those less than 18 or greater than 80-years-old, those with severe multiorgan failure and Acute Physiology and Chronic Health Evaluation (APACHE) II score 25 or greater, patients on mechanical ventilation for more than 72 hours, those who fail enteral feeding, patients who received immunosuppressants 1 week prior to enrollment or who have immunosuppressive disease, or those pregnant or lactating. Patients were randomized into the probiotic group (Medilac-S, China, 0.5 grams three times daily plus standard VAP prevention strategies) or control group (standard VAP prevention strategies only) within 24 hours of intensive care unit (ICU) admission or intubation. The probiotic product used in this study contained *Bacillus subtilis* 4.5×10^9/0.25 g and *Enterococcus faecalis* 0.5×10^9/0.25 g. Investigators defined diagnosis of VAP as infiltrate on chest X-ray that is new, persistent or progressive that has persisted for 48 hours or greater with at least 2 of the following: 1) Temperature > 38 °C or < 35.5 °C; 2) White blood cell count > $12 \times 10^3/mm^3$ or < $3 \times 10^3/mm^3$ and/or left shift; 3) Tracheal aspirates

that are purulent. The primary endpoint was incidence of VAP confirmed by microbiology in patients mechanically ventilated for 48 hours or longer and colonization with potentially pathogenic microorganisms (PPMOs) in the oropharynx and stomach. Secondary endpoints included days on mechanical ventilation, ICU days, days in the hospital after admission to the ICU, mortality, and days of antibiotic use for VAP, and antibiotic-free days. The probiotic and control groups had no significant differences in baseline characteristics including APACHE II scores. Forty-three patients in the probiotic group were diagnosed with microbiologically confirmed VAP compared to 59 patients in the control group (36.4% vs. 50.4%; p = 0.031). There was no significant difference in clinically diagnosed VAP between the two groups (40.7% vs. 53%; p = 0.059). Patients who received probiotics had a greater probability of not developing VAP (p = 0.004). The use of probiotics resulted in a reduction of 0.28 in risk ratio for VAP (95% CI 0.03-0.47) with number needed to treat of 7 patients to prevent one case of VAP. Patients in the probiotic group experienced longer time to onset of VAP compared to control patients (10.4 vs. 7.5 days; p = 0.022). There was no significant difference between the probiotic and control groups in eradication of PPMO colonization (46.9% vs. 32.1%; p = 0.245) or acquisition of PPMO colonization, defined as colonization that occurred > 24 hours post-enrollment in patients with no colonization at baseline (44.2% vs. 52.8%; p = 0.254). Probiotics did not affect the gastric colonization of PPMOs (27.8% vs. 19.2%; p = 0.756). There was no significant difference in duration of mechanical ventilation, duration of antibiotics for VAP, number of antibiotic-free days, days in the ICU, days in the hospital after ICU admission, ICU mortality, or in-hospital mortality. No adverse events were reported with probiotic use [17].

Barraud, et al. [18] conducted a double-blind, randomized, placebo-controlled trial in one medical ICU to evaluate the effect of prophylactic probiotics in mechanically ventilated patients. Adult mechanically ventilated patients expected to be intubated for at least 2 days were included. One hundred sixty-seven patients were enrolled. Excluded patients were those with expected mechanical ventilation less than 2 days, those less than 18-years-old, pregnancy, immunosuppressed, short bowel disease, or inclusion in other trials. Patients were randomized to receive probiotic or placebo. The probiotic used in this study was 5 Ergyphilus (Nutergia, Capdenac, France) consisting of multiple species (2×10^{10} *Lactobacillus rhamnosus GG, Lactobacillus casei, Lactobacillus acidophilus*, and *Bifidobacterium bifidum*). The primary endpoint was mortality at 28 days and secondary endpoints included 90-day mortality, organ failure reversal, ICU-acquired infections and colonization at day 28, and length of stay in the ICU. ICU-acquired infections included catheter and bloodstream related infections, VAP, and urinary tract infection. VAP was defined as presence of infiltrate on chest x-ray with at least one of the following: temperature 38.3 °C or greater, white blood cell count 10,000 uL^{-1} or greater, or purulent tracheal secretions; in addition, VAP definition required positive quantitative pulmonary secretion cultures through bronchoalveolar lavage. Catheter-related bloodstream infection was defined as positive blood culture with same organism in catheter tip culture. Both groups had similar baseline characteristics. No significant difference in 28-day mortality was observed between groups (25.3% probiotic vs. 23.7% placebo; p = 0.80). Mortality at 90 days was similar in both probiotic and placebo groups (31% vs. 30%; p = 0.90). Probiotics did not affect ICU or hospital length of stay or organ failure reversal. A decreased incidence of catheter-related bloodstream infections was observed in the probiotic group (1.84 vs. 6.78 catheter-days; p = 0.005). The number of patients with catheter-related bloodstream infections was less in the probiotic group (3.4% vs. 13.7%; p = 0.005). There was no difference in urinary tract infections, VAP, or combined ICU-acquired infections. Probiotic use did not affect colonization with multi-drug resistant bacteria. In a subgroup analysis, patients with severe sepsis who received probiotics experienced a reduction in 28-day mortality (odds ratio 0.38; 95% CI 0.16-0.93; p = 0.035). No adverse effects were observed [18].

Morrow, et al. [19] used *Lactobacillus rhamnosus* GG in 146 mechanically ventilated patients at high risk for developing VAP. One hundred forty-six patients were included in this prospective, randomized, double-blind, placebo-controlled trial and received either oropharyngeal or gastric administration of probiotic or inulin-based placebo. Patients were included if they were 19 years of age or older and at high risk for requiring mechanical ventilation for at least 72 hours. Those excluded were patients at risk for probiotic infection, pregnant, immunosuppressed, prosthetic cardiac valve, vascular graft, history of rheumatic fever, endocarditis, congenital cardiac abnormality, cardiac trauma, gastroesophageal or intestinal injury, oropharyngeal mucosal injury, or tracheostomy. The primary outcome was VAP based on bronchoalveolar lavage culture in patients who have been intubated for at least 48 hours. Secondary outcomes were mortality, time to VAP, mechanical ventilation duration, hospital and ICU length of stay, *Clostridium difficile* associated diarrhea, ICU-associated diarrhea, use of antibiotics, and hospital charges. Patients treated with probiotic experienced less VAP (19.1% vs. 40%; p = 0.007). Patients who received probiotics received less days of antibiotics for VAP (5.6 vs. 8.6; p = 0.05) and *Clostridium difficile* associated diarrhea (0.5 vs. 2.1; p = 0.02). Patients receiving probiotics also experienced less *Clostridium difficile* associated diarrhea (5.8% vs. 18.6%; p = 0.02). The duration of diarrhea was similar between groups. There were no significant differences in mortality, duration of mechanical ventilation, hospi-

tal and ICU length of stay, or hospital charges between the two groups [19].

In contrast to the previously described studies, Knight, et al. [20] investigated enteral synbiotics and VAP incidence in mechanically ventilated patients. Patients included in this prospective, randomized, placebo-controlled trial were those who were mechanically ventilated and predicted to require intubation for at least 2 days and had no contraindications for enteral nutrition. Exclusion criteria were those less than 16 years of age, immunosuppressed, pregnant, transferred from another institution, greater than 24-hour intubation following ICU admission, or inclusion in another clinical trial. Patients assigned to the synbiotic group received Synbiotic 2000 FORTE (Medipharm, Kagerod, Sweden and Des Moines, IA) which contains *Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei* (10^{10} bacteria per sachet) and betaglucan, inulin, pectin, and resistant starch (prebiotics). VAP was defined as infiltrate on chest X-ray plus at least 2 of the following criteria, more than 48 hours after intubation: temperature greater than 38 °C, white blood cell count greater than 12×10^3 uL^{-1} or less than 4×10^3 uL^{-1}, or purulent tracheobronchial secretions. Primary outcome was VAP incidence and secondary outcomes were ventilator days, oropharyngeal flora, VAP rates/1,000 ventilator days, length of study and mortality in the ICU, and hospital mortality. Baseline characteristics amongst the 259 patients were similar. VAP incidence was similar in the synbiotic and placebo groups (9% vs. 13%; p = 0.42). No significant differences in ventilator days, VAP episodes/1000 ventilator days, length of ICU stay, ICU or hospital mortality were observed between groups. The use of synbiotics did not affect the microbial species or colonization rates of potential pathogens. No adverse effects were reported [20].

A prospective, randomized, placebo-controlled trial investigated whether oral probiotic containing *Lactobacillus* had an effect on *Pseudomonas aeruginosa (P. aeruginosa)* gastric or respiratory tract colonization or infection in intensive care unit (ICU) patients. Inclusion criteria included patients 18 years or older with greater than 48 hours stay in the hospital and a nasogastric feeding tube. Exclusion criteria included patients younger than 18 years of age, immunosuppression, absolute neutrophil count less than 500/mm^3, GI bleeding, contraindication to enteral feeding, and isolation of *P. aeruginosa* from gastric aspirates or the respiratory tract within the first 4 days of admission to the hospital. There were 106 subjects in the placebo arm and 102 subjects in the probiotic arm. Patients randomized into the probiotic arm received 10^9 colony-forming units of *Lactobacillus casei rhamnosus* twice daily through a nasogastric tube from the third day of admission to discharge. Results showed that *P. aeruginosa* colonization or infection was significantly delayed in the probiotic arm compared to the placebo arm (11 vs. 50 days, respectively; p = 0.01). Although not significant, there was a reduction in *P. aeruginosa* VAP cases in the probiotic arm compared to the placebo arm (2.9% vs. 7.5%, respectively). This study was done in a single hospital and had a small sample size. The investigators were not able to recruit the target sample size of 150 subjects in each group in order to meet 90% power. A multi-center study with a larger sample size is needed to confirm the results of this pilot study [21].

A prospective, randomized, placebo-controlled, open-label study conducted in a single hospital in Brazil investigated the effects of prebiotics, probiotics, and synbiotics on VAP and other nosocomial infection rates in the ICU setting. Patients randomized into the trial were those greater than 18 years of age, taking enteral nutrition and under mechanical ventilation. Reasons for exclusion from the trial were use of fibers or probiotics in the last month, clinically significant immunosuppression, active hematologic neoplasia, use of corticosteroids at a dose greater than or equal to 1 mg/kg of prednisone in the last 3 months, use of immunosuppressants, pregnancy, and acquired immunodeficiency syndrome (AIDS). Subjects randomized into the prebiotic, probiotic, and synbiotic arms received soybean polysaccharide (14 g/L), *Lactobacillus johnsonii* (10^9 UFC twice daily), and soybean polysaccharide with *lactobacillus johnsonii* through a nasoenteric tube, respectively. The primary endpoint was colonization of the gastrointestinal (GI) tract and trachea by aerobic pathogenic bacteria. The secondary endpoint was the rate of nosocomial infections up to 30 days after admission. There was no significant difference in either the primary or secondary endpoints between the treatment arms. There was a total of 50 subjects enrolled in the study which is much less than 32 subjects needed in each arm to detect a reduction in gastric colonization [22]. Therefore, it is difficult to make conclusions from these results as the sample size was not met.

Another prospective, randomized, single-centered, active-controlled clinical trial investigated whether *Lactobacillus plantarum* 299 (Lp299) would be as effective as chlorhexidine 0.1% (CHX) in reducing pathogenic bacterial load in the oropharynx of tracheally intubated patients. This study did not look at VAP rates. Patients were included in the study if they were at least 18 years of age with an anticipated need for mechanical ventilation for at least 24 hours. Patients were excluded if they met the following criteria: pneumonia upon admission, terminally ill, fractures in the facial skeleton or the base of skill, mouth ulcers, immunodeficient, human immunodeficiency virus positive, or viral hepatitis. There was no statistically significant difference in bacterial load in the oropharynx when these two arms were compared at baseline and follow-up (p = 0.13). Unlike the aforementioned studies, the sample size of 20 patients in each arm was met to detect a difference. Although this trial was not designed to test difference in VAP rates,

investigators did find a difference in pathogenic enteric bacteria colonization between the two arms. The percent of subjects with pathogenic enteric bacterial growth were 38% and 65% in the Lp299 and CHX arms, respectively [23]. The goal of probiotic use in this scenario is the reduce pathogenic bacteria and reduce VAP rates. Whether these results translate to reduction in VAP rates is uncertain. A new study design with a larger sample size is needed to test for this endpoint.

A systematic review and meta-analysis of the effect of probiotics on nosocomial pneumonia incidence in critically ill patients was performed by Liu, et al. [24] and published in 2012. Twelve randomized controlled trials with a total of 1,546 patients were included. Of the 12 studies, 4 were general ICUs, 8 surgical ICUs, 1 liver transplant patients, and 1 severe acute pancreatitis patient. A significant reduction in nosocomial pneumonia was observed with probiotic use (odds ratio 0.75, 95% CI 0.57-0.97; p = 0.03; I^2 = 46%). There was no effect of probiotics on in-hospital mortality (odds ratio 0.93, 95% CI 0.5-1.74; p = 0.82; I^2 = 51%). Additionally, there was no difference in ICU mortality or duration of hospital or ICU stay. There was no difference in diarrhea or abdominal cramp incidence between probiotic and placebo groups [24]. Barraud, et al. [25] conducted a meta-analysis evaluating the effect of prebiotics, probiotics, or synbiotics on mortality in ICU patients. Thirteen studies were included. Most studies included medical and surgical patients. Five studies had only trauma or surgical patients. Four studies included *Lactobacillus plantarum* 299, *Lactobacillus rhamnosus* GG in one, and a combination of strains in 8 studies. Probiotics did not reduce hospital (odds ratio 0.90; 95% CI 0.65-1.23) or ICU (odds ratio 0.85; 95% CI 0.63-1.15) mortality; neither did they reduce mechanical ventilation duration or hospital length of stay. Probiotics did however reduce ICU-acquired pneumonia (odds ratio 0.58; 95% CI 0.42-0.79) and were associated with reduced ICU length of stay (-1.49 days; 95% CI -2.12 to -0.87 days). However, studies included in these meta-analyses varied in pneumonia definition, patients included, populations studied, types and doses of probiotics used, and therapy duration [25].

Guideline Recommendations

In a search of critical care and infectious disease clinical guidelines available through the Society of Critical Care Medicine and Infectious Diseases Society of America, one published guideline discusses probiotics in critically ill patients. According to the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient published in 2016, probiotics are not recommended for routine use for the general ICU patient population; however, the guidelines suggest using probiotics in select medical and surgical patients who may benefit based on available evidence. The guidelines cite some studies demonstrating benefit of probiotics including prevention of VAP, antibiotic-associated diarrhea, and pseudomembranous colitis in certain patient populations such as liver transplant, trauma, or pancreatectomy. The guidelines suggest probiotics be considered for patients with severe acute pancreatitis who are receiving early enteral nutrition with the potential reduction in infection and hospital length of stay [26].

Future Directions

In a search of the clinicaltrials.gov website, 6 registered clinical trials that are investigating the effects of probiotics in critically ill patients with pneumonia were found: 1 terminated, 3 completed, 2 recruiting [27]. Omic disciplines such as metabolomics may play a role in understanding the interaction between probiotics and microflora in the future. Metabolomics, the study of metabolites and metabolic changes in response to stimuli such as drugs and nutrients, may provide insights into the mechanism behind probiotics, the metabolic changes they produce in the body, and their associated health benefits [28-30].

Discussion and Conclusion

The studies reviewed in this article were mostly conducted in single-centers with a small sample size. The populations of critically ill patients are heterogeneous making it difficult to extrapolate these results for more widespread use. Although the use of probiotics for the prevention of pneumonia in critically ill patients seem promising, there are a few serious concerns. Probiotics are regulated as a dietary supplement by the U.S. Food and Drug Administration, therefore, the manufacturer is not required to prove efficacy or safety of the probiotic before it is marketed to the public [31]. For this reason, it is difficult to know with certainty the quantity and the quality of the bacteria in probiotics. Also, there is no established standard dose or duration of therapy for probiotics and its various uses. These confounders make it difficult to examine the use probiotics for prevention and treatment of disease, including pneumonia in critically ill patients.

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