Probiotics in the critically ill: A systematic review of the randomized trial evidence

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Objective: **Critical illness results in changes to the microbiology of the gastrointestinal tract, leading to a loss of commensal flora and an overgrowth of potentially pathogenic bacteria. Administering certain strains of live bacteria (probiotics) to critically ill patients may restore balance to the microbiota and have positive effects on immune function and gastrointestinal structure and function. The purpose of this systematic review was to evaluate the effect of probiotics in critically ill patients on clinical outcomes.**

Design: **Systematic review.**

Interventions: **None.**

Measurements and Main Results: **We searched computerized databases, reference lists of pertinent articles, and personal files from 1980 to 2011. We included randomized controlled trials enrolling critically ill adults, which evaluated probiotics compared to a placebo and reported clinically important outcomes (infections, mortality, and length of stay). A total of 23 randomized controlled trials met inclusion criteria. Probiotics were associated with reduced infectious complications as documented in 11 trials (risk ratio 0.82; 95% confidence interval 0.69–0.99; $p = .03$; test for heterogeneity $p = .05$; I^2 44%). When data from the seven trials reporting ventilator-associated pneumonia were pooled, ventilator-associated pneumonia rates were also significantly reduced with probiotics (risk ratio 0.75; 95% confidence interval 0.59–0.97; $p = .03$; test for heterogeneity $p = .16$; I^2 35%). Probiotics were associated with a trend toward reduced intensive care unit mortality (risk ratio 0.80; 95% confidence interval 0.59–1.09; $p = .16$; test for heterogeneity $p = .89$; I^2 0%) but did not influence hospital mortality. Probiotics had no effect on intensive care unit or hospital length of stay. Compared to trials of higher methodological quality, greater treatment effects were observed in trials of a lower methodological quality.**

Conclusions: **Probiotics appear to reduce infectious complications including ventilator-associated pneumonia and may influence intensive care unit mortality. However, clinical and statistical heterogeneity and imprecise estimates preclude strong clinical recommendations. Further research on probiotics in the critically ill is warranted. (Crit Care Med 2012; 40:0–0)**

The human gastrointestinal tract contains millions of bacteria that are strongly influenced by the overall health state of the host (1). Many characteristics of the critically ill patient (e.g., hypotension, decreased intestinal motility, increased levels of stress hormones, medications, and altered nutrient intake) influence the composition and phenotype of intestinal microorganisms, leaving the host susceptible to opportunistic pathogens that thrive in an environment wherein the normal protective enteric microorganisms have been eradicated (2–4).

During critical illness, the numbers of Bifidobacteria and Lactobacillus decrease markedly, whereas opportunistic pathogens such as *Pseudomonas aeruginosa* increase logarithmically (5). Hence, there has been much interest in the concept of using endogenous bacteria to help correct the microbial imbalance or "intestinal dysbiosis," which occurs during critical illness. Probiotics are "live microorganisms that when administered in adequate amounts confer a health benefit on the host" (6, 7) and prebiotics are "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria that can improve host health" (8, 9). Synbiotics, as the name implies, are a combination of both probiotics and prebiotics administered together.

There is a strong scientific rationale for the use of probiotics in the intensive care unit (ICU) setting. Probiotics have been shown to contribute to host defense by priming the dendritic cells of the immune system, by producing bactericidal products that kill other pathogens, and by inhibiting the colonization of pathogenic bacteria (10–13). However, randomized trials in critically ill patients are conflicting with evidence of both benefit (14) and harm (15–17), and more research is needed before the use of probiotics can be extended safely to critically ill patients (18). Recent systematic reviews of probiotics are not specific to the critically ill population (19–21) and while four reviews examined critically ill patients, one reported on ventilator-associated pneumonia (VAP) only (22), one included elective surgery patients (23), and two included patients with severe acute pancreatitis (24, 25), making it difficult to draw conclusions for heterogeneous ICU patients. Furthermore, several new trials have been published since these reviews (16, 26–30). The purpose of this systematic review is to critically appraise and summarize the randomized trials of probiotics that enrolled critically ill patients to estimate their effect on clinical outcomes.

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METHODS

Study Identification

Four databases (EMBASE, MEDLINE, CINAHL, and the Cochrane Controlled Trials Register and Database of Systematic Reviews) were searched for articles from 1980 until September 2011. No language restrictions were placed on the searches. The literature search incorporated words such as "probiotics" and "synbiotics"; "nutritional support" or "dietary supplementation" or "enteral nutrition" or "parenteral nutrition" or "peripheral parenteral nutrition" or "total parenteral nutrition" or "nutritional support team" or "nutritional requirements" or "nutritional assessment," or "parenteral nutrition solutions" and "critical care" or "critical illness," or "intensive care units." We also searched personal files and reference lists of relevant review articles.

Eligibility Criteria

To be included in this systematic review, the following four inclusion criteria had to be met: 1) study design: randomized controlled trial; 2) patient population: adult (>18 yrs of age) critically ill patients; 3) intervention: probiotics compared to a placebo; and 4) outcomes: infectious complications and other clinical outcomes such as diarrhea, mortality, ICU, and hospital length of stay. We defined a critically ill patient as a patient cared for in an ICU environment who had an urgent or life-threatening complication (high baseline mortality rate ≥5%) to distinguish them from patients with elective surgery who are also cared for in some ICUs but have a low baseline mortality rate (<5%).

Studies were excluded if they were pseudorandomized, if they enrolled pediatric/adolescent populations, if prebiotics were administered alone, if the effect of probiotics could not be clearly elicited due to multiple interventions, and if none of our *a priori* defined outcomes was reported. Data published in abstract form only were included if additional information about study design was obtained from the authors.

Study Selection and Data Collection

Decisions about the inclusion of the articles were made in duplicate. Titles and abstracts were screened, and the full text review/abstraction was done in duplicate. This review included an assessment of the criteria for inclusion, details on the patient population, intervention and control/placebo, abstraction of methodological quality, and clinical outcomes.

Outcomes

The primary outcome of interest was the number of patients who developed any infectious complication as defined by the primary authors. As some investigators reported rates of VAP, we also examined this outcome separately. Secondary outcomes included ICU mortality, hospital mortality, and length of stay in ICU and in hospital. Mortality specified at either 28 days or 90 days was not considered to be either ICU or hospital mortality, respectively; however, if the mortality time frame was not specified as either ICU or hospital, it was presumed to be the latter. Where reported in sufficient numbers, specific types of infections were also considered as additional outcomes.

Risk of Bias Assessment

The methodological quality of individual studies was assessed independently and in duplicate using a scoring system that we have used in previous reviews with a maximum possible score of 14 (see Appendix 1) (18). Disagreement was resolved by consensus. We attempted to contact the authors of included studies and requested relevant information not contained in published articles.

Data Synthesis

We combined data from all studies to estimate the pooled risk ratio (RR) and associated 95% confidence intervals (CI) for infectious complications, VAP and ICU, and in-hospital mortality. We used the pooled weighted mean difference with 95% CIs to estimate the effect on ICU and hospital length of stay. Pooled RRs were calculated using the Mantel-Haenszel estimator, whereas weighted mean differences were estimated by the inverse variance approach. The random effects model of DerSimonian and Laird (31) was used to estimate variances for the Mantel-Haenszel and inverse variance estimators. When only one group had no events, then one half was added to each cell to allow estimation of the RR. The presence of heterogeneity was tested by a weighted Mantel-Haenszel chi-squared test and quantified by I^2. The possibility of publication bias was assessed by generating funnel plots and testing asymmetry of outcomes using methods proposed by Rücker et al (32). We considered $p < .05$ to be statistically significant. All analyses were conducted in RevMan 5.1 (33) except for the test for asymmetry which was performed using the meta package (34) implemented in R (35).

Subgroup Analyses

Anticipating significant heterogeneity in our primary outcome, we defined, *a priori*, five subgroup analyses to examine the possible causes of heterogeneity. Data from trials that did not clearly specify the species of probiotics used were excluded from the subgroup analyses pertaining to type or dose of probiotics.

1. High dose vs. lower dose: Although good dose-response data are lacking in adults, a recent systematic review in a pediatric population found probiotic doses of 5 billion colony forming units (CFU)/day or greater were more effective than lower doses in reducing diarrhea (36). Accordingly, we compared trials that used a high dose of probiotics defined as >5 billion CFU/day vs. lower dose probiotics defined as <5 billion CFU/day, postulating a larger treatment effect when higher doses were used.
2. *Lactobacillus plantarum* vs. non-*L. plantarum*: *L. plantarum* has known anti-inflammatory effects in the gut (37) and may enhance intestinal barrier function (38). We compared trials that used *L. plantarum* to those that did not, postulating a larger treatment effect in the former group.
3. *Lactobacillus rhamnosus* strain GG (LGG) vs. non-LGG: LGG exerts beneficial effects on intestinal epithelial cells, up-regulates the production of cytoprotective heat shock proteins (39), and has been shown to promote wound healing (40). Thus, we compared those trials that used LGG to those that did not, postulating a larger treatment effect in the former group.
4. Higher mortality vs. lower mortality: Given that probiotics may offer some advantage in patients with severe systemic inflammatory response syndrome (41), we compared studies of patients with higher mortality vs. a lower mortality. Mortality was considered to be high or low based on whether it was greater or less than the median control group mortality of all the trials. In contrast to severity scores that predict the probability of mortality, this approach was used as it is more representative of the actual mortality. We postulated a larger treatment effect in patients at higher risk of death.
5. Higher methodological quality vs. lower methodological quality trials: As methodological quality of trial can influence trial findings (42), we postulated that trials with lower methods scores may demonstrate a greater treatment effect than trials with higher methods scores. We divided trials into two groups based on the median quality score.

RESULTS

Our systematic search yielded 61 potentially eligible randomized controlled trials. Of these, 23 trials (14–16, 26–30, 43–57) were included in the systematic review. The following 39 publications

were excluded for the following reasons: the interventions were not conducted in critically ill patients (58–77); multiple interventions were tested (78–80); probiotics were administered intravenously (81); probiotics were administered as oral swabs (82); the report was published in abstract only and additional information not available from authors (83–85); the report was a meta-analysis or systematic review (19–25); or a duplicate publication of included trials (86–89).

In Tables 1 and 2, we report details on the trial interventions and outcomes. Of 23 included trials, 15 enrolled heterogeneous critically ill (medical and surgical) ICU patients (14, 16, 26, 27, 29, 43, 45–48, 50, 51, 55–57), four enrolled patients with acute pancreatitis (15, 28, 53, 54), one enrolled trauma patients (52), one enrolled head injury patients (30), and two enrolled burn patients (44, 49).

Table 1 also describes the patient population, the methodological score, and the intervention of all included trials. Standard enteral nutrition with or without placebo was given in the control group of 17 trials, whereas six trials incorporated prebiotics into the control feeds.

The mean methodological score of all trials was 9.5 (range 6–13) of a possible 14. Randomization was concealed in seven of 23 (30%) trials, intention to treat analysis was performed in 14 of 23 (61%) trials, and double blinded in 18 of 23 (78%) trials. Of the 23 trials, only seven (30%) tested the viability of the probiotics used in the intervention.

Different probiotic therapies were used among the 23 included trials; eight used *L. plantarum* (14, 47, 50–52, 54, 56, 57) and three trials used LGG (16, 27, 29) (refer to Table 1 for more details on the probiotics used).

Meta-Analyses

Overall Infections and VAP. Infectious complications were reported in 11 trials. Pooled results show that probiotics were associated with a reduction in infectious complications (RR 0.82; 95% CI 0.69–0.99; $p = .03$; test for heterogeneity $p = .05$; I^2 44%; see Fig. 1). When the data from the seven trials reporting VAP were pooled, there was a significant reduction in VAP rates associated with probiotics (RR 0.75; 95% CI 0.59–0.97; $p = .03$; test for heterogeneity $p = .16$; I^2 35%; see Fig. 2).

Mortality. Probiotics had no effect on hospital mortality when the data from 14 trials were pooled (RR 0.97; 95% CI 0.79–1.20; $p = .80$; test for heterogeneity $p = .91$; I^2 0%; see Fig. 3). Probiotics were associated with a trend toward reduced ICU mortality pooling results from six trials (RR 0.80; 95% CI 0.59–1.09; $p = .16$; test for heterogeneity $p = .89$; I^2 0%; see Fig. 4).

Length of Stay. Probiotics had no impact on hospital LOS when data from 11 trials were pooled (weighted mean difference −0.68; 95% CI −4.46 to 3.11; $p = .73$; test for heterogeneity $p = .73$; I^2 69%). Similarly, there was no effect on ICU LOS when results of 12 trials were pooled (weighted mean difference −3.45; 95% CI −9.0 to 2.11; $p = .22$; test for heterogeneity $p < .00001$; I^2 94%). There was no clear asymmetry suggesting publication bias when data for infection, mortality, or length of stay were analyzed ($p > .05$, figures not shown).

Other Outcomes. The impact on diarrhea, reported variably as days of diarrhea, diarrhea rates, and/or duration of diarrhea, was reported in 12 trials. Pooling results from eight trials that reported patients who developed diarrhea, probiotics had no effect (RR 0.95; 95% CI 0.80–1.13; $p = .54$; test for heterogeneity, $p = .39$; I^2 5%). Data were too sparse to aggregate other reported individual infections (see Table 2).

Subgroup Analyses

Dose of Probiotics. Subgroup analyses showed similar rates of infectious complications in trials using high-dose probiotics ($\geq 5 \times 109$ CFU/day) (0.89; 95% CI 0.73–1.09; $p = .26$) as those using a lower dose ($< 5 \times 10^9$ CFU/day) (RR 0.40; 95% CI 0.11–1.50; $p = .18$; p value for the difference between groups, $p = .24$).

Lactobacillus plantarum. Subgroup analyses showed that *L. plantarum*, either alone or in combination with other probiotics, was associated with a significant reduction in overall infections (RR 0.70; 95% CI 0.50–0.97; $p = .03$). However, this was not significantly different from the aggregated results of trials that did not include *L. plantarum* (RR 0.90; 95% CI 0.72–1.12; $p = .35$; p value for the difference between groups $p = .20$).

Lactobacillus rhamnosus GG. Subgroup analyses showed that the effect of trials using LGG was not different from trials that did not include LGG (RR 0.86; 95% CI 0.67–1.10 compared to RR 0.77; 95% CI 0.57–1.04; p value for the difference between groups $p = .59$).

Higher Mortality. The median mortality rate (hospital mortality or ICU mortality if hospital not reported) in the control groups of all studies was 14%. Subgroup analyses showed that probiotics were associated with a trend toward reduction in overall infections among patients with higher risk of death (>14% mortality in the control group) (RR 0.75; 95% CI 0.56–1.01; $p = .06$). There was no significant effect observed for trials of patients with a lower mortality in the control group (RR 0.88; 95% CI 0.66–1.18; $p = .40$) and the test of subgroup differences was not significant (p value for the difference between groups, $p = .46$).

Methodological Score. The median method score was 10. We compared trials with a methods score of <10 with those with a score of ≥10. Trials with a higher score showed no effect on infection (RR 0.96; 95% CI 0.77–1.19; $p = .69$), whereas trials with a lower methods score showed a significant reduction in infectious complications (RR 0.70; 95% CI 0.58–0.85; $p = .0003$, p value for the difference between groups $p = .03$) (Fig. 5).

DISCUSSION

In this systematic review of randomized trials of critically ill patients, probiotics were associated with lower rates of infections, including VAP, and a trend toward reduced ICU mortality. Probiotics had no effect on hospital mortality, ICU or hospital length of stay, or diarrhea. Data in this review were too sparse for other specific individual infections, which precluded statistical aggregation. Our findings are tempered by the presence of significant clinical and statistical heterogeneity and the lack of statistical precision in some analyses. The inferences we can make from these findings are further weakened by an important subgroup result, suggesting treatment effects that are associated with trials of a lower methodological quality.

Bearing in mind the important limitations above, our findings are consistent with a 2009 publication of five trials that demonstrated that probiotics were associated with a significant reduction in VAP (22). Our systematic review, the largest to date (n = 23), is the most current as it contains recently published studies and is most comprehensive in its assessment of treatment effect, in that it examines the effect of probiotics on multiple clinical endpoints (not just VAP).

Although the exact mechanisms by which probiotics act remain to be elucidated, probiotics adhere well to

Table 1. Characteristics of included randomized controlled trials

No	Author, yr	Population (n)	Methods Score	Type of Probiotic/Intervention		
				Delivery Vehicle	Intervention/Dose/Duration	Control
1	Tempé, 1983	ICU patients (n = 40)	C Random: yes; ITT: yes; blinding: double; score: 10; viability (intervention): NR	EN tube	EN (unknown) + Ultra-Levure (*Saccharomyces boulardii*), 10^{10}/1-L solution for 11–21 days	EN (unknown) + placebo (sterile solution)
2	Schlotterer, 1987	Burn patients (n = 18)	C Random: no; ITT: no; blinding: double; score: 8; viability (intervention): NR	NG tube	EN (Polydiet or Nutrigil) + *Saccharomyces boulardi*, 500 mg QID for 8–28 days	EN (Polydiet or Nutrigil) + placebo
3	Heimburger, 1994	Mixed ICU patients, 83% received antibiotics (n = 62)	C Random: no; ITT: no; blinding: double; score: 9; viability (intervention): NR	EN tube	EN (standard) + 1 g of Lactinex (*Lactobacillus acidophilus* and *Lactobacillus bulgaricus*), 2×10^6 TID for 5–10 days	EN (standard) + placebo (0.5 g dextrose + 0.5 g lactose)
4	Bleichner, 1997	Mixed ICU patients (n = 128)	C Random: not sure; ITT: yes; blinding: double; score: 13; viability (intervention): NR	EN tube	EN (unknown) + *S. boulardii*, 500 mg QID for 21 days or until EN stopped	EN (unknown) + placebo (powder)
5	Kecskes, 2003	ICU patients on antibiotics (n = 45)	C Random: no; ITT: no; blinding: double; score: 8; viability (intervention): yes	NJ tube	EN (Nutrition Fiber) + fermented oatmeal formula with *Lactobacillus plantarum* 299×10^9 BID and fiber for 7 days	EN (Nutrition Fiber) + heat killed *Lactobacillus plantarum* 299 BID + fiber (nonviable)
6	Jain, 2004	ICU patients (n = 90)	C Random: no; ITT: yes; blinding: double; score: 10; viability (intervention): NR	Oral or NG tube	EN or PN + Trevisone capsule TID + 7.5 g Raftilose (oligo-fructose), BID until hospital discharge	EN or PN + placebo (powdered sucrose capsules)
7	Lu, 2004	Burn patients (n = 40)	C Random: no; ITT: yes; blinding: double; score: 9; viability (intervention): NR	NR	EN + synbiotics (four types of probiotics and four types of unspecified prebiotics) for 21 days	EN + four types of prebiotics
8	Klarin, 2005	Critically ill patients on antibiotics (n = 17)	C Random: no; ITT: no; blinding: no; score: 6; viability (intervention): NR	Mixed in fermented oatmeal, given via NG tube	EN + *Lactobacillus plantarum* 299v, 10^9/day 50 mL every 6 hrs × 3 days then 25 mL every 6 hrs until ICU discharge	EN (Impact or Nutrodrip Fibre). Some patients needed PN
9	McNaught, 2005	ICU patients on antibiotics (n = 130)	C Random: no; ITT: yes; blinding: no; score: 7; viability (intervention): NR	Oral, NJ tube	EN or PN + Proviva (oatmeal and fruit drink) 5×10^7 CFU/mL of *L. plantarum* 299v ×500 mL until hospital discharge or beyond	EN or PN alone
10	Kotzampassi, 2006	Multiple trauma patients from five ICUs (n = 77)	C Random: no; ITT: no; blinding: double; score: 8; viability (intervention): NR; VAP determination: clinical	Endoscopic gastrostomy or NG tube	EN or PN + Synbiotic 2000 Forte 10^{11}, one sachet/day for 15 days until ICU discharge	EN or PN + placebo (Maltodextrin), mixed in tap water
11	Alberda, 2007	ICU patients (n = 28)	C Random: no; ITT: yes; blinding: double; score: 10; viability (intervention): no for VSL#3; yes for bacteria sonicates	NG tube	Jevity Plus (EN) (10 g fructooligosaccharides/1000 mL and 12 g of soluble and insoluble fiber blend) + VSL#3, one package BID, 9×10^{11}/day for 7 days until ICU discharge or EN discontinuation	Jevity Plus + Placebo
12	Li, 2007	Severe acute pancreatitis patients (n = 25)	C Random: no; ITT: yes; blinding: no; score: 7; viability (intervention): NR	Given enterally	Jinshuangqi (bifidobacteria, *lactobacillus*, and *streptococcus*) 2.0 g TID on the basis of traditional treatment; duration: NR	Traditional treatment
13	Olah, 2007	Severe acute pancreatitis patients (n = 83)	C Random: no; ITT: no; blinding: no; score: 9; viability (intervention): NR	NJ tube	EN (Nutrition Fiber) + Synbiotic 2000, 4×10^{10} CFU for 7 days	EN (Nutrition Fiber) + 10 g plant fibers (2.5 g each of betaglucan, inulin, pectin, and resistant starch) (prebiotics) BID for at least 2 days
14	Forestier, 2008	Mixed ICU patients, 50% on antibiotics (n = 208)	C Random: not sure; ITT: no; blinding: double; score: 8; viability (intervention): NR; VAP determination: objective	NG tube or oral (after tube removal)	*Lactobacillus casei rhamnosus*, 10^9 CFU BID until ICU discharge	Placebo (growth medium never exposed to bacteria)

Table 1.—*Continued*

No	Author, yr	Population (n)	Methods Score	Type of Probiotic/Intervention		
				Delivery Vehicle	Intervention/Dose/Duration	Control
15	Besselink, 2008	Acute pancreatitis patients from 15 ICUs (n = 298)	C Random: not sure; ITT: yes; blinding: double; score: 11; viability (intervention): NR; VAP determination: clinical	NJ tube or oral	EN (Nutrition Multifiber) + Ecologic 641, 10^{10} CFU BID for 28 days	EN (Nutrition Multifiber) + placebo (cornstarch + maltodextrins)
16	Klarin, 2008	ICU patients from five ICUs, on antibiotics for *Clostridium difficile* (n = 68)	C Random: yes; ITT: no; blinding: double; score: 10; viability (intervention): NR	Mixed in fermented oatmeal added to enteral feeds NG tube	299 *Lactobacillus plantarum*, 8×10^{8} CFU/mL given as 6×100 mL doses every 12 hrs and after 50 mL given BID until ICU discharge	Same oatmeal gruel mixed with lactic acid
17	Knight, 2009	General ICU patients (n = 300)	C Random: yes; ITT: no; blinding: double; score: 10; viability (intervention): NR; VAP determination: clinical	NJ or orogastric tube	EN (Nutrition Energy) + Synbiotic 2000 Forte, 4×10^{11} species/sachet, BID for 28 days or ICU discharge	EN (Nutrition Energy) + placebo
18	Barraud, 2010	Mechanically ventilated ICU patients, 80% on antibiotics (n = 167)	C Random: yes; ITT: yes; blinding: double; score: 12; viability (intervention): NR; VAP determination: objective	NG tube	EN (Fresubin) + Ergyphilus, 2×10^{10} per capsule + potato starch 5 caps/day for 28 days	EN (Fresubin) + placebo capsules (excipient of potato starch)
19	Morrow, 2010	ICU patients (n = 146)	C Random: no; ITT: yes; blinding: double; score:10; viability (intervention): yes; VAP determination: objective	Oropharynx and NG tube	EN (routine care) + *Lactobacillus rhamnosus* GG, 2×10^{9} BID as lubricant and mixed with water until extubation	EN (routine care) + inert plant starch inulin (prebiotic) BID as a lubricant and mixed with water
20	Frohmader, 2010	General ICU patients on antibiotics (n = 45)	C Random: yes; ITT: yes; blinding: double; score: 11; viability (intervention): yes	NG or NJ tube	EN (standard) + VSL#3, mixed in nutritional supplement (Sustagen), BID until hospital discharge	EN (standard) + placebo mixed in nutritional supplement (Sustagen), BID
21	Ferrie, 2011	Critically ill patients with diarrhea, (n = 36)	C Random: no; ITT: yes; blinding: double; score: 10; viability (intervention): yes	NG tube	EN (standard) + Culturelle (*Lactobacillus rhamnosus* GG), 10^{10} species/capsule + 280 mg inulin powder for 7 days	EN (standard) + Raftiline, gelatin capsule with 280 mg inulin powder (prebiotic)
22	Sharma, 2011	Acute pancreatitis patients (n = 50)	C Random: yes, ITT: yes; blinding: double; score: 11; viability (intervention): yes	Oral, NJ, or NG	EN (standard) or oral, four sachets each 2.5×10^{9}, *Lactobacillus acidophilus, Bifidobacterium longum*, *Bifidobacterium bifidum*, and *Bifidobacterium infantis* + 25 g fructose for 7 days	EN (standard) + placebo
23	Tan, 2011	Closed head injury patients (n = 52)	C Random: yes, ITT: yes; blinding: single; score:10; viability (intervention): yes; VAP determination: clinical	NG tube	EN (standard), total of 10^{9} bacteria, i.e., seven sachets each 0.5×10^{8} *Bifidobacterium longum*, 0.5×10^{7} L *Lactobacillus bulgaricus* and 0.5×10^{7} *Streptococcus thermophilus* for 21 days	EN (standard)

ICU. intensive care unit; C Random, concealed randomization; ITT, intention to treat; NR, not reported; EN, enteral nutrition; NG, nasogastric; NJ, nasojejunal; PN, parenteral nutrition; CFU, colony forming units; VAP, ventilator-associated pneumonia; BID, twice daily; TID, three times a day; QID, four times a day.

Trevis: one capsule = *Lactobacillus acidophilus* La5, *Bifidobacterium lactis* Bb12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, 4×10^{9}/total.

Synbiotic 2000 Forte: 10^{11} CFU of each: *Pediococcus pentoseceus* 5-33:3, *Leuconostoc mesenteroides* 32–77:1, *Lactobacillus paracasei* ssp. *paracasei* 19, *L. plantarum* 2362 and 2.5 g each of inulin, oat bran, pectin, and resistant starch.

Ergyphilus: 10^{10} *Lactobaccilus rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidu*.

VSL#3: $>10^{10}$ *Bifidobacterium longum*, *Bifidobacterium breve*, $>10^{10/g}$ *Bifidobacterium infantis*, $>10^{11/g}$ *Lactobacillus acidophulus*, *plantarum*, *casei*, *bulgaris*, and *Streptococcus thermophilus*.

Jinshuangqi: *Bifidobacterium longum* $>10^{7}$ CFU, *Lactobacillus bulgaricus* $>10^{6}$ CFU, and *Streptococcus Thermophilus* $>10^{6}$ CFU.

Ecologic 641: *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Lactococcus lactis*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis*.

Synbiotic 2000: 10^{10} CFU of each: *Pediococcus pentoseceus* 5-33:3, *Leuconostoc mesenteroides* 32–77:1, *L. paracasei* ssp. *paracasei* 19, *L. plantarum* 2362, and 2.5 g each of betaglucan, inulin, pectin, and resistant starch.

Table 2. Clinical outcomes of included randomized controlled trials

No	Author, yr	Mortality (%)		Infections (%)	
		Intervention	Control	Intervention	Control
1	Tempé, 1983	3/20 (15)	3/20 (15)	NR	NR
2	Schlotterer, 1987	NR	NR	NR	NR
3	Heimburger, 1994	NR	NR	NR	NR
4	Bleichner, 1997	NR	NR	NR	NR
5	Kecskes, 2003	Hospital 1/22 (5)	Hospital 2/23 (9)	Septic complications 1/22 (5)	Septic complications 7/23 (30)
6	Jain, 2004	Hospital 22/45 (49)	Hospital 20/45 (45)	Septic complications 33/45 (73)	Septic complications 26/45 (58)
7	Lu, 2004	Hospital 2/20 (10)	Hospital 1/20 (5)	Infectious complications 8/20 (40)	Infectious complications 11/20 (55)
8	Klarin, 2005	ICU 1/8 (12), Hospital 2/8 (25)	ICU 2/7 (29), Hospital 2/7 (29)	NR	NR
9	McNaught, 2005	18/52 (35)	18/51 (35)	Septic morbidity 21/52 (40)	Septic morbidity 22/51 (43)
10	Kotzampassi, 2006	ICU 5/35 (14)	ICU 9/30 (30)	Infections 22/35 (63) VAP 19/35 (54), septic complications 17/35 (49), central venous line infections 13/35 (37), wound infections 6/35 (17), UTI 6/35 (17)	Infections 27/30 (90), VAP 24/30 (80), septic complications 23/30 (77), central venous line infections 20/30 (66), wound infections 8/30 (26), UTI 13/30 (43)
11	Alberda, 2007	ICU 1/10 (10)	ICU 1/9 (11)	NR	NR
12	Li, 2007	NR	NR	Infections 8/14 (58)	Infections 10/11 (91)
13	Olah, 2007	Hospital 2/33 (6)	Hospital 6/29 (21)	Infections 9/33 (27), septic complications 7/33 (12), pancreatic abscess 2/33 (6), infected pancreatic necrosis 2/33 (6), UTI 3/33 (9)	Infections 15/29 (52), septic complications 17/29 (28), pancreatic abscess 2/29 (7), infected pancreatic necrosis 6/29 (21), UTI 3/33 (9)
14	Forestier, 2008	NR	NR	VAP 19/102 (19)	VAP 21/106 (20)
15	Besselink, 2008	24/152 (16)	9/144 (6)	Infections 46/152 (30), VAP 24/152 (16), bacteremia 33/152 (22), infected necrosis 21/152 (14), urosepsis 1/52 (2)	Infections 41/144 (28), VAP 16/144 (11), bacteremia 22/144 (15), infected necrosis 14/144 (10), urosepsis 2/144 (1)
16	Klarin, 2008	ICU 2/22 (9), hospital 3/22 (5)	ICU 2/22 (9), hospital 2/22 (0)	NR *C. difficile* + fecal samples 0/71	NR *C. difficile* + fecal samples 4/80
17	Knight, 2009	ICU 28/130 (22), hospital 35/130 (27)	ICU 34/129 (26), hospital 42/129 (33)	VAP 12/130 (9)	VAP 17/129 (13)
18	Barraud, 2010	ICU 21/87 (24), 28 days 22/87 (25), 90 days 27/87 (31)	ICU 21/80 (26), 28 days 19/80 (24), 90 days 24/80 (30)	All infections 30/87 (34), infection >96 hrs 26/87 (30), VAP 23/87 (26), catheter-related BSI 3/87 (4), UTI 4/87 (5)	All infections 30/80 (38), infection >96 hrs 29/80 (36), VAP 15/80 (19), catheter-related BSI 11/80 (14), UTI 4/89 (5)
19	Morrow, 2010	12/68 (18)	15/70 (21)	VAP 13/73 (18)	VAP 28/73 (38)
20	Frohmader, 2010	5/20 (25)	3/25 (12)	NR	NR
21	Ferrie, 2011	Hospital 2/18 (11), 6 months 7/18 (39)	Hospital 2/18 (11), 6 months 5/18 (28)	Infections 14/18 (78)	Infections 16/18 (89)
22	Sharma, 2011	Hospital 2/24 (8)	Hospital 2/26 (8)	NR	NR
23	Tan, 2011	28 day 3/26 (12)	28 day 5/26 (19)	Infections 9/26 (35), VAP 7/26 (27)	Infections 15/26 (58), VAP 13/26 (50)

NR, not reported; ICU, intensive care unit; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; BSI, blood stream infection.

Length of Stay (Range)		Diarrhea (%)	
Intervention	Control	Intervention	Control
NR	NR	Diarrhea days 34/389 (9)	Diarrhea days 63/373 (17)
NR	NR	Diarrhea days 3/150 (2)	Diarrhea days 19/143 (13)
NR	NR	Diarrhea 5/16	Diarrhea 2/18
NR	NR	Diarrhea 18/64 (28)[106], days with diarrhea 91/648 (14)	Diarrhea 24/64 (38), days with diarrhea 134/683 (20)
Hospital 13.7 ± 8.7	Hospital 21.4 ± 17.9	NR	NR
Hospital 24.0 ± 31.5, ICU 11.9 ± 13.1	Hospital 18.7 ± 13.5, ICU 9.0 ± 8.9	NR	NR
NR	NR	NR	NR
Hospital 48.3 ± 30.4, ICU 14.2 ± 10.6	Hospital 34.3 ± 15.4, ICU 16.3 ± 15.7	NR	NR
ICU 5 (2–9)	ICU 4 (2–7)	NR	NR
ICU 27.7 ± 15.2	ICU 41.3 ± 20.5	Diarrhea 5/35 (14)	Diarrhea 10/30 (30)
NR	NR	Diarrhea 1/10 (14)	Diarrhea 2/9 (23)
Hospital 42 ± 5.0	Hospital 49 ± 6.8	NR	NR
Hospital 14. 9 ± 3.3	Hospital 19.7 ± 4.5	NR	NR
ICU 22.5 ± 20.6	ICU 19.7 ± 16.7	NR	NR
ICU 6.6 ± 17, hospital 28.9 ± 41.5	ICU 3.0 ± 9.3, hospital 23.5 ± 25.9	Diarrhea 25/152 (16)	Diarrhea 28/144 (19)
Hospital 25.8 ± 19.4, ICU 8.0 ± 5.4	Hospital 50.3 ± 75.2, ICU 11.6 ± 14	NR	NR
ICU 6 (3–11)	ICU 7 (3–14)	Diarrhea 7/130 (5)	Diarrhea 9/129 (7)
Hospital 26.6 ± 22.3, ICU 18.7 ± 12.4	Hospital 28.9 ± 26.4, ICU 20.2 ± 20.8	Diarrhea 48/87 (55)	Diarrhea 42/80 (53)
ICU 14.8 ± 11.8, hospital 21.4 ± 14.9	ICU 14.6 ± 11.6, hospital 21.7 ± 17.4	Non–*C. difficile* diarrhea 42/68 (62), *C. difficile* diarrhea 4/68 (6)	Non–*C. difficile* diarrhea 44/70 (63), *C. difficile* diarrhea 13/70 (19)
ICU 7.3 ± 5.7	ICU 8.1 ± 4	Diarrhea episodes/pt/day 0.53 ± 0.54	Diarrhea episodes/pt/day 1.05 ± 1.08
ICU 32.04 ± 24.46, hospital 54.50 ± 31.26	ICU 29.75 ± 18.81, hospital 59.04 ± 33.92	Duration of diarrhea 3.83 ± 2.39, loose stools/day 1.58 ± 0.88	Duration of diarrhea 2.56 ± 1.85, loose stools/day 1.10 ± 0.79
Hospital 13.23 ± 18.19, ICU 4.94 ± 9.54	Hospital 9.69 ± 9.69, ICU 4.0 ± 5.86	NR	NR
ICU 6.8 ± 3.8	ICU 10.7 ± 7.3	NR	NR

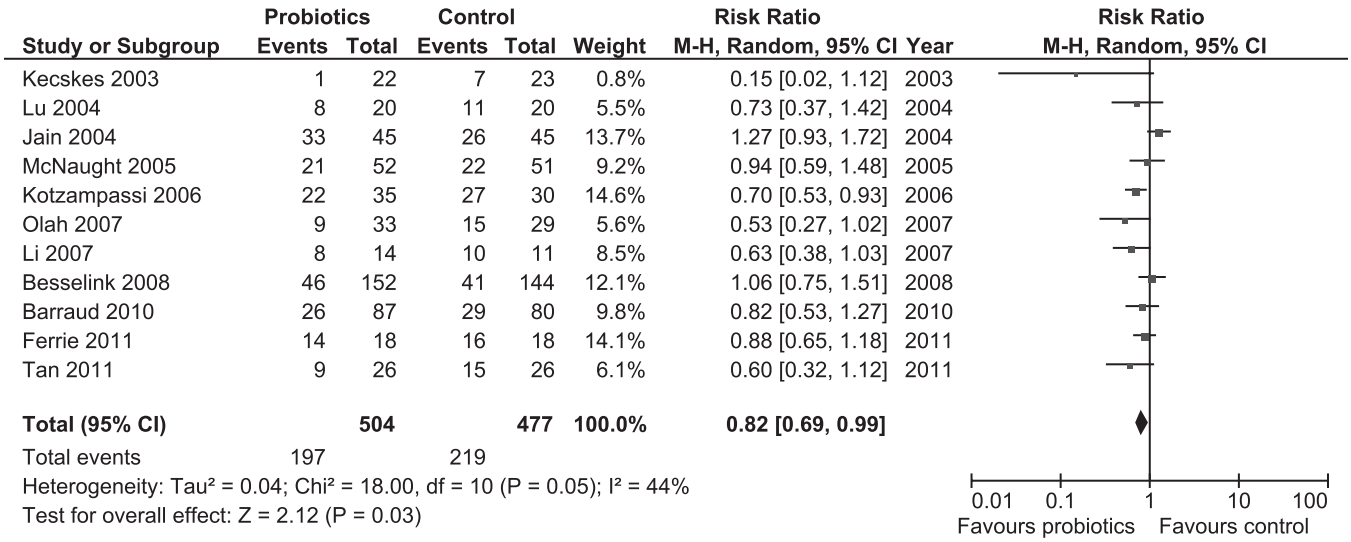

Figure 1. Effect of probiotics on infections. *CI*, confidence interval; *M-H*, Mantel-Haenszel.

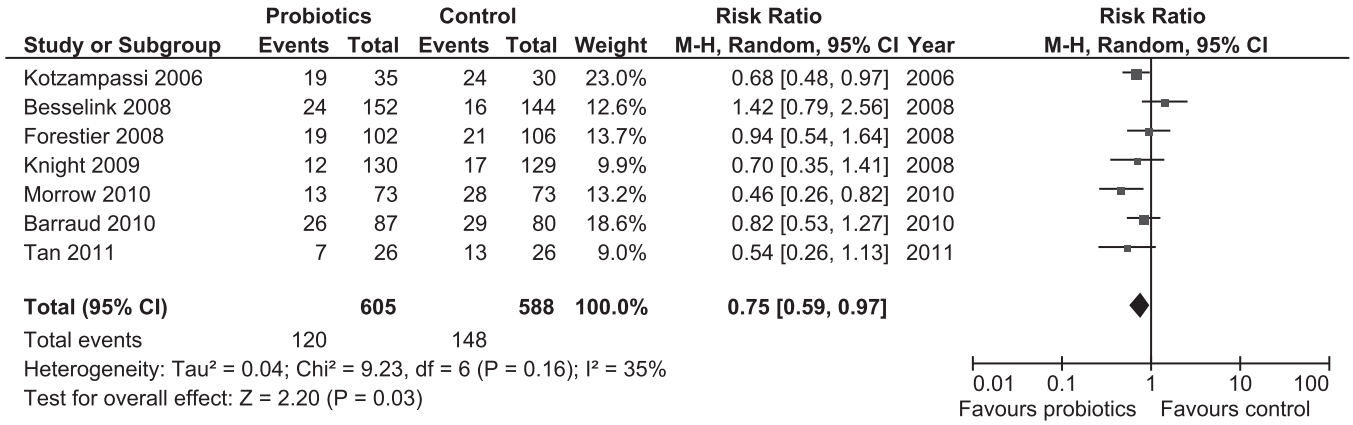

Figure 2. Effect of probiotics on ventilator-associated pneumonia. *CI*, confidence interval; *M-H*, Mantel-Haenszel.

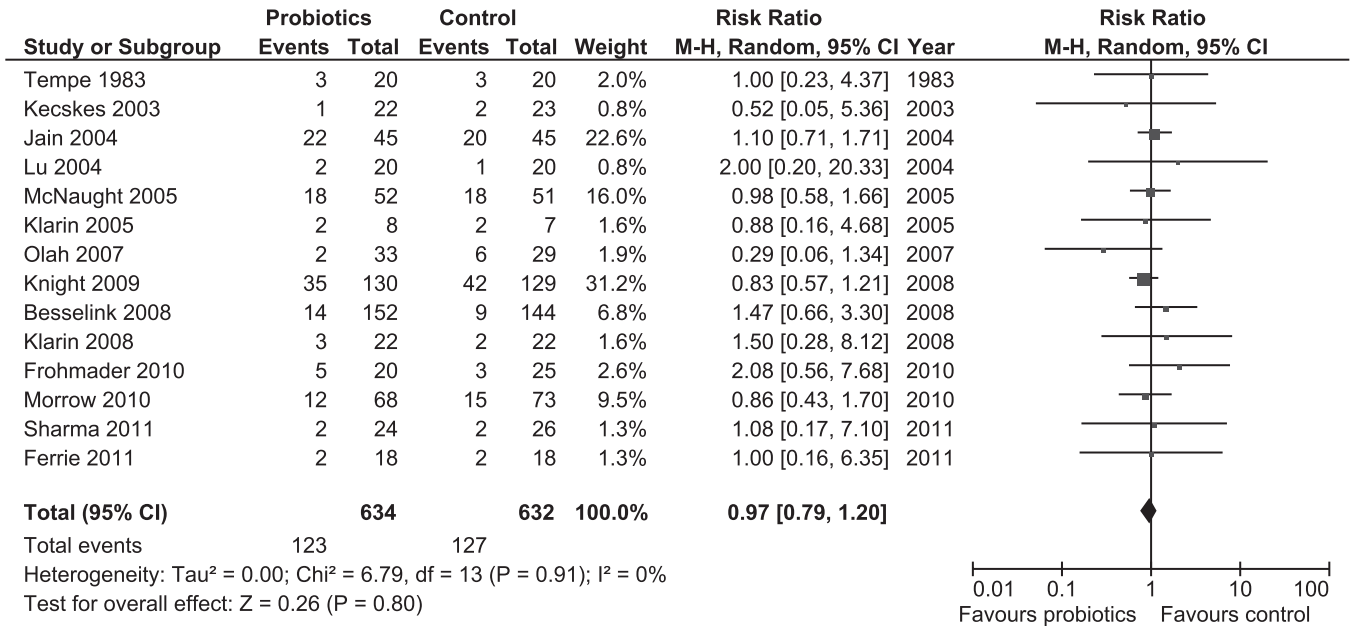

Figure 3. Effect of probiotics on hospital mortality. *CI*, confidence interval; *M-H*, Mantel-Haenszel.

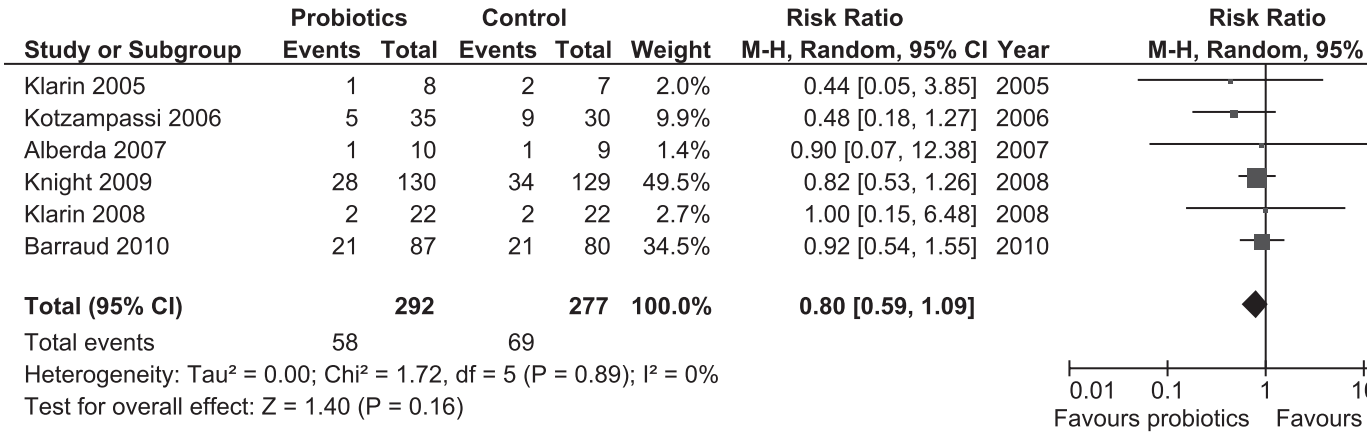

Figure 4. Effect of probiotics on intensive care unit mortality. *CI,* confidence interval; *M-H*, Mantel-Haenszel.

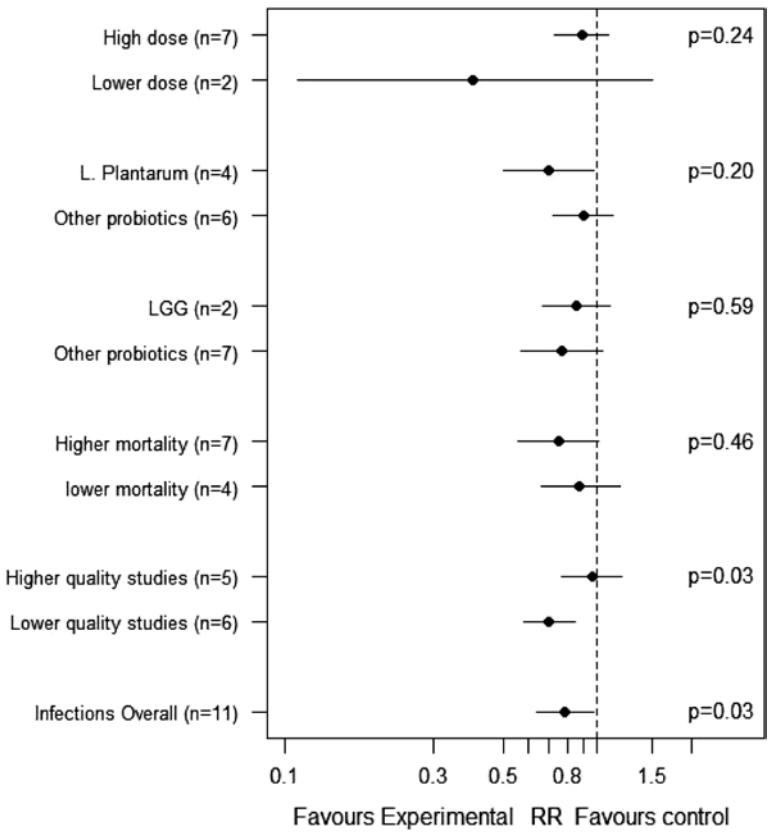

Figure 5. Results of subgroup analyses of the effect of probiotics on infection. Numbers in brackets indicate the number of studies. *p* values for the subgroups indicate the differences in the subgroup effect of probiotics on infections. *LGG*, *Lactobacillus rhamnosus* GG; *RR*, risk ratio.

epithelial cells, augment host immune response, and prevent colonization of pathogenic bacteria (90–92). They also exert effects on the enteric and autonomic nervous system, which in turn may play a role in their mechanisms of action (93, 94).

Many studies suggest probiotics may reduce antibiotic-associated diarrhea and *Clostridium difficile* infections (95–98). Our data showed no reduction in diarrhea, consistent with another recent report of critically ill patients that showed a similar lack of impact on the overall incidence of diarrhea (22). It is tempting to speculate that the choice of probiotic and site of action may play an important role; for example, probiotics that act at the small intestine may confer different effects on the host than those that act primarily at the colon (93, 94). Strains that confer effects primarily on the large intestine may be expected to have the largest impact on antibiotic-associated diarrhea. Not all trials in this review examined diarrhea as an outcome, and our analysis is underpowered regarding the impact on *C. difficile*–associated diarrhea.

Although no benefit was suggested with respect to mortality, we also observed no harm conferred by probiotics. Several case studies have been published on iatrogenic probiotic infections (usually bloodstream infections), particularly with the use of *Saccharomyces*-based probiotics (99–102). Yet, none of the trials we included reported any catheter-related infections or bacteremia caused specifically by the probiotic organisms. One trial (15) reported bacteremia in both groups; however, no probiotic organisms were isolated in any of the bacteremias from the probiotic group. In another trial (52), central line infections were less frequent in the probiotics group (37% vs. 66%, $p = .02$). Specific organisms were not identified, but in the list of "most frequently isolated organisms from septic foci" data, probiotic organisms were not reported. In a third trial (16), no bacteremias with probiotic organisms were reported and there was a significant decrease in catheter-related bloodstream infections in the probiotic treatment group (3.4% vs. 13.7%; $p = .005$). Although we found no evidence to indicate that bacterial probiotics are dangerous in the ICU setting, avoiding administration to patients at high risk of iatrogenic probiotic complications seems prudent (e.g., immunocompromised hosts, patients with indwelling prosthetic materials such as vascular grafts and heart valves). In addition, it should be noted that the yeast *Saccharomyces boulardii* has a product label warning advising against its use in patients with indwelling central line catheters and its use in ICU patients is generally not recommended.

Clinical trials with probiotics pose unique challenges as the effects of probiotics are not only dose-related but are also known to be both strain and species-specific, questioning the validity of combining different probiotics in this meta-analysis (103, 104). We attempted to address these issues by conducting *a priori* subgroup analyses, one of which suggested that trials including *L. plantarum* (RR 0.70) vs. those which do not (RR 0.90) are associated with a greater reduction in infection; however, the difference between these subgroups is not significant ($p = .20$). Nevertheless, several observations support such a biologic rationale. *L. plantarum* inhibits nuclear factor-κB (37), its cell wall components possess anti-inflammatory properties (105), it produces bacteriocins and lantibiotics (e.g., plantaricin C), with antimicrobial properties (106, 107) and it up-regulates mucous production in intestinal epithelial cells, rendering adherence of pathogens more difficult (108). Be that as it may, which probiotics and doses confer the greatest impact remains uncertain.

The probiotic trials to date highlight the potential of this strategy to decrease infectious outcomes, but firm conclusions are not possible as our subgroup analyses suggested that low-quality trials reported larger treatment effects than higher quality trials. Some key details are unreported. Viability testing of the strains of the probiotics used was not always performed. Although some cointerventions are documented such as ancillary VAP prevention strategies, other management strategies such as the type of enteral nutrition were unclear. Such details would be useful because many enteral nutrition formulae are supplemented with nutrients thought to act as prebiotics (i.e., fructooligosaccharides, inulin, and fiber). Considerable variation exists in the populations studied, the interventions tested, the outcomes reported, and the results obtained. For example, the Besselink study was unusual in its design, which entailed infusion of probiotics and prebiotics directly into the jejunum of patients with acute pancreatitis. The level of heterogeneity across studies thus weakens any inferences that can be made from these results.

These limitations notwithstanding, clinical trials to date suggest that probiotics may reduce overall infection rates including VAP in critically ill patients. We view the findings of this systematic review as primarily hypothesis generating, and further research is needed to understand whether any species and/or doses may have greater impact than others. Large rigorous multicenter trials will help generate better estimates of possible benefit and harm, confirming or refuting the findings of clinical trials to date.

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Appendix 1. Methodology scoring

	Score		
	0	1	2
Randomization	Not applicable	Not concealed or not sure	Concealed randomization
Analysis	Other	Not applicable	Intention to treat
Blinding	Not blinded	Single blind	Double blinded
Patient selection	Selected patients or unable to tell	Consecutive eligible patients	Not applicable
Comparability of groups at baseline	No or not sure	Yes	Not applicable
Extent of follow-up	<100%	100%	Not applicable
Treatment protocol	Poorly described	Reproducibly described	Not applicable
Cointerventions	Not described	Described but not equal or not sure	Well described and all equal
Outcomes	Not described	Partially described	Objectively defined