Research Article

**Efficacy of probiotics or synbiotics for critically ill adult patients: a systematic review and meta-analysis of randomized controlled trials**

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**Abstract**

**Background:** Microbial dysbiosis in critically ill patients is a leading cause of mortality and septic complications. Probiotics and synbiotics have emerged as novel therapy on gut microbiota to prevent septic complications. However, current evidence on their effects is conflicting. This work aims to systematically review the impact of probiotics or synbiotics in critically ill adult patients.

**Methods:** A comprehensive search of the PubMed, CBM, Embase, CENTRAL, ISI, and CNKI databases was performed to identify randomized controlled trials that evaluate probiotics or synbiotics in critically ill patients. The quality assessment was based on the modified Jadad’s score scale and the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. The major outcome measure was mortality. Secondary outcomes included incidence of septic complications, sepsis incidence, length of intensive care unit (ICU) stay, incidence of non-septic complication, and ventilator day. Data synthesis was conducted by Review Manager 5.4.

**Results:** A total of 25 randomized controlled trials reporting on 5049 critically ill patients were included. In the intervention group, 2520 participants received probiotics or synbiotics, whereas 2529 participants received standard care or placebo. Pooling data from randomized controlled trials demonstrated a significant reduction in the incidence of ventilator-associated pneumonia (VAP) in the treatment group [(risk ratio (RR) 0.86; 95% confidence interval (CI): 0.78–0.95; p < 0.003, I² = 85%)]. However, in the subgroup analysis, the reduction of incidence of VAP was only significant in patients receiving synbiotics (RR = 0.61, 95% CI: 0.47–0.80, p = 0.0004, I² = 40%) and not significant in those receiving only probiotics (RR = 0.91, 95% CI: 0.82–1.01, p = 0.07, I² = 65%). Moreover, sepsis incidence of critically ill patients was only significantly reduced by the addition of synbiotics (RR = 0.41; 95% CI: 0.22–0.72, p = 0.005, I² = 0%). The incidence of ICU-acquired infections was significantly reduced by the synbiotics therapy (RR = 0.72; 95% CI: 0.58–0.89, p = 0.0007, I² = 79%). There was no significant difference in mortality, diarrhea, or length of ICU stay between the treatment and control groups.
Conclusions: Synbiotics is an effective and safe nutrition therapy in reducing septic complications in critically ill patients. However, in such patients, administration of probiotics alone compared with placebo resulted in no difference in the septic complications.

Key words: Critically ill patients, Probiotics, Synbiotics, Meta-analysis, Systematic review, Mortality, Ventilator-associated pneumonia

Highlights
• Synbiotics are an effective and safe therapy in reducing septic complications in critically ill patients.
• Among critically ill patients, the administration of probiotics alone, compared with placebo, resulted in no difference in septic complications.
• The effect of a mixture of probiotics is better than a single probiotic species.

Background
The gut is one of the most important organs in the human immune system. Moreover, it is also a leading target organ during stress, especially in burn, trauma and shock patients. The gut is known as the ‘motor’ of multiple organ dysfunction and bacterial translocation [1]. The latter is a major cause of mortality in critically ill patients [2,3]. Owing to the limitations of septic control strategies, the frequency of sepsis is increasing in intensive care units (ICUs). Protecting the commensal microbiota and gut function is becoming a novel strategy to reduce the risk of septic complications in critically ill patients in Europe [4].

Probiotics are live microorganisms that are beneficial to the host when administered in adequate quantities. Commensal microbiota are a vital barrier component of the intestine, helping prevent the spread of pathogens. Intestinal resistance could decrease because of deteriorating commensal microbiota in critically ill patients. Probiotics are commonly used as microbial nutritional supplements to maintain the balance of the intestinal microbiota [5,6]. On the other hand prebiotics are non-digestible foods that can benefit the host by stimulating the activity of selective dominant bacteria in the colon [7,8]. Synbiotics are a combination of probiotics and prebiotics in a single preparation. In 1990, supplementation with probiotics or synbiotics emerged as a potential therapy geared towards reducing the incidence of septic complications in critically ill patients.

The efficacy of probiotics and synbiotics has been demonstrated in elective surgery [9,10]. They are effective in treating diarrhea in patients with systemic inflammatory response syndrome (SIRS) [11,12]. Beneficial microbiota continue to decrease while pathogens increase in the intestines of patients with SIRS, which is the leading cause of decreased short-chain fatty acids (SCFAs). The pH of the gut mucosa can increase, which could further deteriorate the gut microbiota. This vicious cycle promotes the progression of SIRS and septic complications [11,13]. The hypothesized mechanism of probiotics or synbiotics breaks the vicious circle by increasing beneficial microbiota and altering the gut environment. Many randomized controlled trials (RCTs) have evaluated the effects of probiotics or synbiotics in reducing septic complications in critically ill patients, but their conclusions have been mixed. Some studies have shown that probiotics or synbiotics are more effective than placebo treatments in reducing mortality and the incidence of ventilator-associated pneumonia (VAP) [14,15]. However, other studies find probiotics useless or even engendering adverse effects [16–19]. Clinicians are puzzled by the conflicting nature of the evidence. A systematic review and meta-analysis to synthesize the current evidence is needed for practitioners faced with the decision of using probiotics or synbiotics. In this systematic review of RCTs, we examined the effects of probiotics or synbiotics on mortality and septic complications in critically ill patients.

Methods

Literature retrieval strategy
RCTs were identified from PubMed (US National Library of Medicine 1990–2021), Web of Science, The Cochrane Library (2021, Issue 11), China Knowledge Resource Integrated Database (CNKI), World Health Organization (WHO) Global Index Medicus and Chinese Biomedicine Database (CBM). Search terms were connected by AND/OR and included patients (adult critically ill patients and those with trauma), interventions (probiotic, prebiotic and synbiotic) and comparisons (placebo and standard treatment). References from RCTs were browsed and corresponding authors were consulted for any further information that may have been acquired by them but not been reported publicly. Ongoing RCTs were checked using clinical trial registers. The complete terms and strategies for identifying the articles (Table S1, see online supplementary material).

Inclusion and exclusion criteria
RCTs evaluating probiotics or synbiotics in adult critically ill patients (APACHE II scores >10) were included. Non-RCTs and RCTs that included pregnant women or patients younger than 18 years of age were excluded. Studies that did not address any primary or secondary outcomes, as previously mentioned, were excluded.
Table 1. Methodological characteristics of studies included

| Study                          | Population           | PE (n) | PA(n) | Groups | Concealment | Blinding          | Probiotic                                      | Prebiotic | Symbiotic | Placebo/SC | Route | DoT | M.J.S. |
|-------------------------------|----------------------|--------|-------|--------|-------------|-------------------|------------------------------------------------|-----------|-----------|------------|-------|-----|--------|
| Alberda et al., 2007 [25]     | Critically ill patients MV>2d | 19     | 28    | 3      | Identical packaging | Double blinded | *Lactobacillus casei, L. plantarum, Lactobacillus acidophilus and Lactobacillus delbrueckii subsp. Bulgaricus, Bifidobacterium longum, B. breve and B. Infantis, Streptococcus salivarius* subsp. T | –         | –         | Placebo NG/NJ | 7d    | 7/7 |        |
| Arruda et al., 2004 [26]      | TBI, GCS5–12         | 20     | 20    | 2      | NR          | NR                | *Lactobacillus johnsonii* | –         | –         | SC NG/NJ | 5d    | 5/7 |        |
| Barraud et al., 2010 [27]     | Critically ill patients MV>2d | 167    | 167   | 2      | Envelopes   | Double blinded | *Mainly Lactobacillus rhamnosus GG, but also L. casei, L. acidophilus and Bifidobacterium bifidum* S. bouardi | –         | –         | Placebo NG/NJ | 7d    | 7/7 |        |
| Bleichner et al., 1997 [28]   | Critically ill patients | 128    | 128   | 2      | NR          | Double blinded | *L. rhamnosus GG* | –         | –         | Placebo NG | 7d    | 7/7 |        |
| Ferrie et al., 2011 [29]      | Critically ill patients | 27     | 27    | 2      | Identical packaging | Double blinded | Lactobacillus | –         | –         | Placebo NG | 7d    | 7/7 |        |
| Forestier et al., 2008 [30]   | Critically ill patients | 208    | 208   | 2      | Envelopes   | Double blinded | *Lactic acid bacteria, lyophilized Bifidobacterium breve, B. longum, Bifidobacterium infantis, L. acidophilus, Lactobacillus plantum, L. casei, L. bulgaricus, Streptococcus thermophilus* | –         | –         | Placebo NG/NJ | 7d    | 7/7 |        |
| Frohmader et al., 2010 [31]   | Critically ill patients | 45     | 45    | 2      | Envelopes   | Double blinded | *Synbiotic 2000Forte* | –         | –         | Placebo NG | 13d   | 7/7 |        |
| Giamarellors-Bourboulis et al., 2009 [32] | Severe multiple injuries MV>2d | 72     | 72    | 2      | Envelopes   | Double blinded | *Symbiotic 2000Forte* | –         | –         | Placebo NG | 13d   | 7/7 |        |
| Jain et al., 2004 [33]        | Critically ill patients | 90     | 90    | 2      | Identical packaging | Double blinded | *(L. acidophilus Placebo L.a5, Bifidobacterium lactis Bb-12, S. thermophilus and L. bulgaricus)* and prebiotic oligofructose | –         | –         | Oral or NG | 10d   | 7/7 |        |

(Continued)
| Study                        | Population                          | PE (n) | PA (n) | Groups | Concealment | Blinding         | Probiotic                        | Prebiotic | Symbiotic | Placebo/SC | Route | DoT | M.J.S. |
|-----------------------------|-------------------------------------|--------|--------|--------|-------------|-----------------|----------------------------------|-----------|-----------|------------|-------|-----|--------|
| Johnstone et al., 2021 [18] | Critically ill patients MV > 3d     | 1318   | 1332   | 2      | Envelopes   | Double blinded  | L. rhamnosus GG                 | –         | –         | Placebo   | Oral  | 60d | 7/7    |
| Klarin et al., 2005 [34]    | Critically ill patients MV > 3d     | 15     | 15     | 2      | Envelopes   | Double blinded  | L. plantarum 299 (Lp299)         | –         | –         | Placebo   | NG    | 7d  | 6/7    |
| Klarin et al., 2008 [35]    | Critically ill patients MV > 1d     | 44     | 44     | 2      | Envelopes   | Double blinded  | L. plantarum 299 (Lp299)         | –         | –         | SC        | NG    | 12d | 6/7    |
| Knight et al., 2009 [36],   | critically ill patients MV > 2d     | 259    | 259    | 2      | NR          | Double blinded  | –                                | –         | –         | Symbiotic 2000 Forte | Placebo | 10d | 5/7    |
| Kozlowski et al., 2006 [37] | Trauma critically ill patients      | 65     | 65     | 2      | NR          | Double blinded  | –                                | –         | –         | Placebo   | NG    | 15d | 5/7    |
| Litton, 2021 [38]           | Critically ill patients MV > 3d     | 110    | 108    | 2      | Unblinded pharmacist Envelopes | Double blinded | L. plantarum 299 (Lp299)         | –         | –         | Placebo   | Oral or NG | 60d | 7/7    |
| Lopez de Toro et al., 2014  | Multi-organ failure                | 89     | 89     | 2      | NR          | Double blinded  | –                                | –         | –         | Symbiotic drink | Placebo | 7d  | 7/7    |
| Mahmoodpoor et al., 2019    | Critically ill patients MV > 2d     | 100    | 100    | 2      | NR          | Double blinded  | Lactobacillus species (casei, acidophilus, rhamnosus, bulgaricus), Bifidobacterium species ( breve, longum) and S. thermophilus | –         | –         | Placebo   | NG/NJ | 14d | 7/7    |
| Mcnaught et al., 2005 [40]  | Critically ill patients MV > 3d     | 103    | 103    | 2      | NR          | Double blinded  | L. rhamnosus GG                 | –         | –         | SC        | Oral or NG    | 9d  | 5/7    |
| Morrow et al., 2010 [41]    | Critically ill patients MV > 3d     | 138    | 138    | 2      | NR          | Double blinded  | L. rhamnosus GG                 | –         | –         | Placebo   | NG    | 14d | 5/7    |
| Rongrungruang et al., 2015  | Critically ill patients MV > 3d     | 150    | 150    | 2      | NR          | Double blinded  | L. casei (Shirota strain)        | –         | –         | Placebo   | Oral or NG    | 12d | 4/7    |
| Sanek et al., 2014 [43]     | Critically ill patients MV > 3d     | 40     | 40     | 2      | NR          | Double blinded  | Lactic acid bacteria, lyophilized B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. casei, L. bulgaricus, S. thermophilus | –         | –         | Placebo   | NG    | 7d  | 5/7    |
| Shimizu et al., 2018 [14]   | Critically ill patients             | 72     | 72     | 2      | NR          | Single blinded  | –                                | –         | –         | B. breve strain, L. casei strain and galactooligosaccharides | SC       | NG  | 20d | 5/7    |
| Spindler-Vesel et al., 2007  | Multiple injured patients           | 52     | 113    | 4      | NR          | NR               | –                                | –         | –         | Symbiotic 2000 Forte | SC       | NG  | 14d | 4/7    |
| Tan et al., 2011 [45]       | TBI, GCS 5–8                        | 43     | 43     | 2      | NR          | Single blinded  | B. longum, Lactobacillus bulgaricus, S. thermophilus. live Bacillus subtilis and Enterococcus faecalis (Medilac-S) | –         | –         | Placebo   | NG    | 21d | 5/7    |
| Zeng et al., 2016 [15]      | Critically ill patients MV > 2d     | 235    | 235    | 2      | Envelopes   | Double blinded  | –                                | –         | –         | SC        | NG    | 14d | 7/7    |

PA participants analyzed, PE participants enrolled, DoT duration of treatment, NG nasogastric, NJ nasojejunal, NR not reported, SC standard care, M.J.S. modified Jadad score, TBI Traumatic brain injury, GCS Glasgow Coma Scale, MV mechanical ventilation.
The intervention groups received probiotics or synbiotics through any approach, preparation or duration. Participants with severe acute pancreatitis were excluded from the study. Control groups administered standard care or placebo did not receive any synbiotics or probiotics.

Outcome measures
The primary outcome was mortality in critically ill patients. Secondary outcomes included the incidence of VAP, incidence of septic complications, incidence of sepsis, length of ICU stay and non-septic complications.

Selection of studies
Two reviewers (KW and QZ) independently performed electronic literature searches and evaluated the eligibility of the studies based on the inclusion criteria. Relevant studies were initially screened using titles and abstracts. The potential articles were then assessed independently, and any disagreements were adjudicated by a third reviewer (HJ).

Data extraction and analysis
Data were extracted independently by two investigators (KW and QZ) from the full text of the studies and compiled into shared sheets. We collected the following information from the included studies: study identifier (first author and year of publication), duration of treatment, study design, inclusion and exclusion criteria, intervention and number of subjects, and primary and secondary outcomes. Data were validated by a third reviewer (HJ) using a standardized method. The methodological quality assessment shown in Table 1 was based on the Cochrane Reviewers’ Handbook [20] and the modified Jadad scale [21,22]. The risk ratio (RR) was used to report discrete numerical variables along with 95% confidence intervals (CIs). The mean difference (MD) was reported to estimate the continuous outcomes. The $I^2$ statistic was used to quantify the heterogeneity, and forest plots were generated and double-checked by two reviewers (KXL and MWS). If $I^2 < 25\%$, the pooled outcomes were considered to have low statistical heterogeneity, and if $I^2 > 75\%$, the pooled outcomes were considered to have high statistical heterogeneity. Data synthesis was conducted by the Review Manager (RevMan) 5.4 and R (R package version 3.7–0.) software [23]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement to report the research protocol, outcome and relevant items in this systematic review [24].

Results

Studies included
A total of 186 potential studies were identified in the initial literature retrieval. The initial screening resulted in 45 candidate studies. The PRISMA diagram shows the details of the selection process and exclusion criteria (Figure 1). Finally, 25

Figure 1. PRISMA diagram detailing the literature search and the study selection/exclusion process. PRISMA Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCT randomized controlled trials
RCTs [14,15,18,19,25–45] were deemed appropriate for full analysis. The characteristics of the included studies and their designs are listed in Table 1. Of the 25 studies included in the final meta-analysis, 7 used synbiotics as the intervention and the other 18 used probiotic therapy. In total, 5049 patients were included in this meta-analysis, of whom 2520 were randomly treated with probiotic or synbiotic therapy, whereas the remaining 2529 received placebo or standard care.

Patients and interventions

The mean (standard deviation) age of patients who received probiotics or synbiotic treatment was 58.2 (16.8) years and the mean age for those in the control group was 58.8 (17.5) years. A variety of diagnostic categories were included: respiratory, cardiac, neurological, sepsis, trauma, thoracic, acute illnesses and surgery. Of the 18 studies receiving probiotics alone, only 5 used a mixture of probiotics, while the remainder received a single probiotic species (Lactobacillus or Saacharomyces boulardii). Seven studies administered synbiotics using a mixture of probiotics. Eleven studies reported side effects or complications associated with the intervention [14,18,19,25,27–29,31,37,41,42]. There were two serious adverse events reported in a randomized clinical trial [18]. Compared to the placebo or standard treatment group, rates of diarrhea, vomiting, abdominal bloating and abdominal pain were not significantly increased in participants in the treatment group (Table 2).

Major outcome: mortality

Among all the included studies, 22 reported on the primary outcome (mortality) [14,15,18,19,25,27,29,31–45]. There was no heterogeneity among the 22 studies and a fixed model was used for meta-analysis. The mortality of patients

| Study                          | Probiotics   | Symbiotics   | Placebo or standard care | P  |
|-------------------------------|--------------|--------------|--------------------------|----|
| Alberda et al., 2007 [25]     | Diarrhea:1/10| -            | Diarrhea:2/9              | -  |
| Arruda et al., 2004 [26]      | Not stated   | -            | Not stated                | -  |
| Barraud et al., 2010 [27]     | Diarrhea:48/87| -            | Diarrhea:42/80            | -  |
| Blechner et al., 1997 [28]    | Diarrhea:18/36| -            | Diarrhea:24/36            | 0.26|
| Ferrie et al., 2011 [29]      | Diarrhea:2/13 | -            | Diarrhea:2/14             | 0.08|
| Forestier et al., 2008 [30]   | Not stated   | -            | Not stated                | -  |
| Frohmader et al., 2010 [31]   | Diarrhea:5/20 | -            | Diarrhea:3/25             | 0.03|
| Gamairellors-Bourboulis et al., 2009 [32] | - | Not stated | Not stated | - |
| Jain et al., 2004 [33]        | Diarrhea:836/1318 | - | Diarrhea:855/1332 | - |
| Johnstone et al., 2021 [18]   | Adverse events: 13/1318 | - | Adverse events: 1/1332 | 0.001|
| Klarin et al., 2005 [34]      | Not stated   | -            | Not stated                | -  |
| Klarin et al., 2008 [35]      | Not stated   | -            | Not stated                | -  |
| Klarin et al., 2009 [36]      | Not stated   | -            | Not stated                | -  |
| Kotzampassi et al., 2006 [37] | Diarrhea:5/35 | -            | Diarrhea:10/30            | 0.34|
| Litton, 2021 [38]             | Not stated   | -            | Not stated                | -  |
| Lopez de Toro et al., 2014 [39]| -           | Not stated   | Not stated                | -  |
| Mahmoodpoor et al., 2019 [19] | Diarrhea:7/48 | -            | Diarrhea:15/54            | 0.08|
| Mcnaught et al., 2005 [40]    | Not stated   | -            | Not stated                | -  |
| Morrow et al., 2010 [41]      | Clostridium difficile | - | Clostridium difficile | - |
| Rongrungruang et al., 2015 [42]| Diarrhea:19/75| -            | Diarrhea:14/75            | -  |
| Sanaie et al., 2014 [43]      | Not stated   | -            | Not stated                | -  |
| Shimizu et al., 2018 [44]     | Enteritis:2/35 | -            | Enteritis:10/37           | -  |
| Spindler-Vesel et al., 2007 [44] | Not stated | -            | Not stated                | -  |
| Tan et al., 2011 [45]         | Not stated   | -            | Not stated                | -  |
| Zeng et al., 2016 [15]        | Not stated   | -            | Not stated                | -  |
receiving probiotics or synbiotics was not significantly reduced compared to those who received placebo treatment or standard care (RR = 0.94, 95% CI: 0.85–1.04, p = 0.23, I² = 0%) (Figure 2). In the subgroup analysis, there were no significant differences in mortality between patients receiving probiotics and those who received synbiotics.

Septic complications

The incidence of VAP Fourteen studies [14,15,18,19,26,27,30,32,36,37,41,42,44,45] reported data on the incidence of VAP. Quantitative pooling of data revealed a significant reduction in the incidence of VAP in patients receiving probiotics or synbiotics (Figure 3). The risk of developing VAP was reduced in the intervention group (RR = 0.86, 95% CI: 0.78–0.95; p = 0.003; I² = 85%). However, in the subgroup analysis, the reduction in the incidence of VAP was only significant in patients receiving synbiotics (RR = 0.61, 95% CI: 0.47–0.80, p = 0.0004, I² = 40%) and not significant in those receiving only probiotics (RR = 0.91, 95% CI: 0.82–1.01, p = 0.07, I² = 65%).

All ICU-acquired infections and sepsis incidence Twelve RCTs [14,18,26,27,33,37,40,43–45] reported data on the incidence of ICU-acquired infections. Pooling data from RCTs demonstrated that there was no significant difference in the incidence of ICU-acquired infections between the treatment and control groups (RR = 0.92; 95% CI: 0.84–1.01, p = 0.09, I² = 63%) (Figure 4). The I² test revealed a significantly high heterogeneity. We then conducted a subgroup analysis that found that studies using synbiotics might be the source of heterogeneity. Furthermore, in the subgroup analyses of the 5 RCTs [14,33,37,39,44] that administered synbiotics, there was a significant reduction in the incidence of ICU-acquired infections (RR = 0.72; 95% CI: 0.58–0.89, p = 0.0007, I² = 79%). However, in 7 trials [18,26,27,38,40,43,45] that administered probiotics alone, there was no effect on infections (RR = 0.96; 95% CI: 0.87–1.07, p = 0.48; I² = 37%). These results also confirmed the incidence of sepsis. In 2 studies [32,37] that administered synbiotics, there was a significant reduction in the incidence of sepsis (RR = 0.41; 95% CI: 0.22–0.72, p = 0.005, I² = 0%) (Figure 5).

### Table 1

| Study or Subgroup | Experimental Events Total | Control Events Total | Weight | Risk Ratio M.H. Fixed, 95% CI | Risk Ratio M.H. Fixed, 95% CI |
|-------------------|---------------------------|---------------------|--------|-------------------------------|-------------------------------|
| **2.1.1 Probiotics** |
| Alberda 2007       | 10                        | 1                   | 0.2%   | 0.90 [0.07, 12.38]            |
| Barraud 2010       | 21                        | 21                  | 80     | 3.7% [0.54, 1.55]             |
| Ferri 2011         | 12                        | 2                   | 14     | 0.3% [1.08, 1.67]             |
| Frohmader 2010     | 5                         | 20                  | 3      | 0.4% [2.08, 7.08]             |
| Johnstone 2021     | 363                       | 318                 | 1322   | 64.0% [0.96, 1.08]            |
| Klarin 2005        | 2                         | 8                   | 2      | 0.4% [0.88, 4.68]             |
| Klarin 2008        | 2                         | 22                  | 2      | 0.3% [1.00, 15.64]            |
| Lifton 2021        | 4                         | 110                 | 4      | 0.7% [0.98, 3.33]             |
| Mahmoonpoor 2019   | 6                         | 48                  | 8      | 10% [0.90, 2.27]              |
| Menautt 2005       | 18                        | 52                  | 19     | 31% [0.98, 1.60]              |
| Morrow 2010        | 12                        | 68                  | 15     | 70% [0.82, 4.62]              |
| Rongrungraung 2015 | 25                        | 76                  | 20     | 75% [0.96, 1.50]              |
| Sanale S 2014      | 2                         | 20                  | 5      | 0.8% [0.40, 0.99]             |
| Tan 2011           | 3                         | 22                  | 5      | 0.9% [0.57, 2.10]             |
| Zeng 2016          | 15                        | 118                 | 9      | 17% [1.65, 3.78]              |
| **Subtotal (95% CI)** |
| Total events       | 480                       | 500                 |        | 84% [0.96, 1.07]              |
| **2.1.2 Synbiotics** |
| Giannarelli-Bourboulis 2009 | 5       | 36                  | 10     | 36% [0.50, 1.12]              |
| Jain 2004          | 22                        | 45                  | 10     | 3.4% [1.10, 1.71]             |
| Knight 2000        | 28                        | 130                 | 34     | 129% [0.82, 1.26]             |
| Kotrampas 2006     | 5                         | 35                  | 9      | 16% [0.48, 1.27]              |
| Lopez de Toro 2014 | 15                        | 46                  | 14     | 43% [1.00, 1.55]              |
| Shumiz 2018        | 3                         | 35                  | 4      | 37% [0.79, 3.29]              |
| Spindler-reisel 2007 | 2   | 26                  | 2      | 26% [1.08, 0.67]              |
| **Subtotal (95% CI)** |
| Total events       | 80                        | 93                  |        | 0% [0.92, 1.04]               |
| **Total (95% CI)** |
| Total events       | 2344                      | 2339                |        | 100% [0.94, 1.04]             |

Figure 2. Forest plot of pooled weighted mean difference from RCTs evaluating the effect on risk ratio for mortality with probiotics and synbiotics therapy. RCTs randomized controlled trials, CI confidence intervals

Figure 3. Forest plot of pooled weighted mean difference from RCTs evaluating the effect on risk ratio for mortality with probiotics and synbiotics therapy. RCTs randomized controlled trials, CI confidence intervals
Figure 3. Forest plot of randomized controlled trials evaluating the efficacy for reducing the incidence of VAP. VAP = ventilator-associated pneumonia, CI = confidence intervals.

Figure 4. Forest plot of pooled data from RCTs demonstrating the reduction in risk of ICU-acquired infections. RCTs = randomized controlled trials, CI = confidence intervals, ICUs = intensive care units.
Length of ICU stay Data on the length of ICU stay was reported in only 17 studies [14,15,18,27–31,33–36,39–41,43,44]. There was no significant difference in the length of ICU stay between the intervention and control groups (MD: 0.03; 95% CI: −0.26 to 0.32, p = 0.85, I² = 0%) (Figure 6). The same result was obtained in subgroup analysis.

Non-septic complications Some RCTs reported data on non-septic complications. Eleven studies [14,18,19,25,27–29,31,37,41,42] provided a count of the number of patients with diarrhea. Pooling data from RCTs showed no significant difference between the intervention and control groups (RR = 0.99; 95% CI: 0.93–1.07, p = 0.87, I² = 51%) (Figure 7). However, in the subgroup analysis, the reduction
Figure 7. Effect on the incidence of diarrhea with probiotics or synbiotics therapy. CI confidence intervals.

| Study or Subgroup | Experimental Events | Control Events | Total Events | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|----------------|--------------|--------|-------------------------------|-------------------------------|
| 2.5.1 Probiotics  |                     |                |              |        |                               |                               |
| Alberda 2007      | 1                   | 10             | 11           | 9      | 0.27 [0.05, 1.46]             |                               |
| Bavraud 2010      | 48                  | 87             | 135          | 80     | 0.29 [0.05, 1.59]             |                               |
| Bleicher 1997     | 18                  | 36             | 54           | 36     | 0.36 [0.05, 2.24]             |                               |
| Ferrie 2011       | 2                   | 13             | 15           | 14     | 0.22 [0.03, 1.47]             |                               |
| Frohmader 2010    | 5                   | 20             | 25           | 25     | 0.21 [0.03, 1.51]             |                               |
| Johnstone 2021    | 691                 | 1318           | 949          | 1322   | 0.20 [0.03, 1.39]             |                               |
| Mahmoodpoor 2019  | 7                   | 48             | 55           | 52     | 0.27 [0.04, 1.73]             |                               |
| Morrow 2010       | 4                   | 60             | 44           | 70     | 0.17 [0.02, 1.30]             |                               |
| Rongrngrung 2015  | 19                  | 75             | 94           | 75     | 0.34 [0.05, 2.26]             |                               |
| Subtotal (95% CI) | 1675                | 1603           | 3278         | 97.5%  | 0.11 [0.04, 1.08]             |                               |
| Total events      | 795                 | 796            |              |        |                               |                               |
| Heterogeneity: Ch² = 12.47, df = 8 (P = 0.13); I² = 36% |
| Test for overall effect: Z = 0.33 (P = 0.74) |

Figure 8. Subgroup analysis: effects of different bacterial species on incidence of VAP. VSL#3 is a specific mixture of different bacterial species, consisting of four strains of Lactobacillus, three strains of Bifidobacterium and Streptococcus salivarius subsp. CI confidence intervals, VAP ventilator-associated pneumonia.

| Study or Subgroup | Experimental Events | Control Events | Total Events | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|----------------|--------------|--------|-------------------------------|-------------------------------|
| 4.3.1 L. rhamnosus GG |                     |                |              |        |                               |                               |
| Bavraud 2010      | 23                  | 87             | 110          | 80     | 1.41 [0.79, 2.51]             |                               |
| Forestier 2008    | 24                  | 102            | 126          | 106    | 1.04 [0.63, 1.71]             |                               |
| Johnstone 2021    | 209                 | 1318           | 1527         | 1322   | 1.02 [0.68, 1.54]             |                               |
| Morrow 2010       | 17                  | 68             | 85           | 70     | 0.53 [0.33, 0.82]             |                               |
| Subtotal (95% CI) | 1575                | 1578           | 3153         | 70.1%  | 0.99 [0.87, 1.13]             |                               |
| Total events      | 353                 | 356            |              |        |                               |                               |
| Heterogeneity: Ch² = 8.14, df = 3 (P = 0.04); I² = 63% |
| Test for overall effect: Z = 0.09 (P = 0.93) |

4.3.2 L. casei |                     |                |              |        |                               |                               |
| Arruda 2004      | 5                   | 10             | 15           | 10     | 2.13 [0.29, 4.56]             |                               |
| Subtotal (95% CI) | 95                  | 95             | 190          | 6.4%   | 0.72 [0.48, 1.11]             |                               |
| Total events      | 23                  | 32             |              |        |                               |                               |
| Heterogeneity: Ch² = 1.30, df = 1 (P = 0.25); I² = 23% |
| Test for overall effect: Z = 1.52 (P = 0.13) |

4.3.4 VSL#3 |                     |                |              |        |                               |                               |
| Mahmoodpoor 2019  | 31                  | 48             | 79           | 54     | 0.68 [0.55, 0.85]             |                               |
| Tan 2011         | 7                   | 16             | 23           | 13     | 0.64 [0.34, 1.21]             |                               |
| Zeng 2016        | 43                  | 118            | 161          | 117    | 0.72 [0.54, 0.97]             |                               |
| Subtotal (95% CI) | 192                 | 190            | 382          | 23.5%  | 0.70 [0.58, 0.84]             |                               |
| Total events      | 81                  | 123            |              |        |                               |                               |
| Heterogeneity: Ch² = 0.16, df = 2 (P = 0.92); I² = 0% |
| Test for overall effect: Z = 3.81 (P = 0.0001) |

| Study or Subgroup | Experimental Events | Control Events | Total Events | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|----------------|--------------|--------|-------------------------------|-------------------------------|
| 2.3.5 VSL#15 |                     |                |              |        |                               |                               |
| Total (95% CI)    | 1842                | 1853           | 3705         | 100.0% | 0.91 [0.82, 1.01]             |                               |
| Total events      | 457                 | 511            |              |        |                               |                               |
| Heterogeneity: Ch² = 22.98, df = 8 (P = 0.003); I² = 65% |
| Test for overall effect: Z = 1.81 (P = 0.07) |
| Test for subgroup differences: Ch² = 10.23, df = 2 (P = 0.006); I² = 80.4% |
in the incidence of diarrhea was significant in the symbiotic group (RR = 0.33; 95% CI: 0.15–0.72, \( p = 0.006, I^2 = 0\% \)).

**Subgroup analysis depending on probiotics** Considering that different bacterial species may have different effects on critically ill patients, we performed a subgroup analysis depending on probiotics such as *Lactobacillus rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus plantarum* 299 and VSL#3 (a specific mixture of different bacterial species). It may be a better strategy to distinguish between beneficial and unbeneficial probiotics. Subgroup analyses showed that the risk of developing VAP was reduced only by VSL#3 (RR = 0.70, 95% CI: 0.58–0.84, \( p = 0.0001, I^2 = 0\% \)) (Figure 8). *L. rhamnosus* GG and *L. casei* did not reduce the incidence of VAP. None of the other outcomes, including mortality, diarrhea, sepsis, other ICU-acquired infections or length of ICU stay, showed a significant difference among these four types of probiotics.

**Publication bias and sensitivity analysis** It is well known that studies with positive outcomes are easier to publish. Consequently, all valid studies cannot be truly represented merely by those studies that end up being published. A funnel plot was used to assess publication bias. The evaluation of publication bias based on mortality demonstrated no asymmetry in favor of positive studies (Figure 9). Moreover, the risk of the included RCTs is shown in Figure 10. To evaluate the stability of the results, a sensitivity analysis was conducted by excluding one study at a time. The combined RR of risks was confirmed to be consistent and without apparent fluctuations.

**Discussion**

This meta-analysis of pooled data from 25 RCTs revealed that symbiotic therapy significantly reduced the risk of septic complications. Furthermore, the incidence of sepsis in critically ill patients is significantly reduced by the administration of symbiotics. In contrast, probiotic or symbiotic administration had no effect on mortality, length of ICU stay or non-septic complications. The probiotic or symbiotic therapy duration of the included studies was not uniform. The mean (standard deviation) duration was 11.59 (4.75) days. However, the reduction risk of septic complications remained whether the duration was more than 11.59 days or less. Thus, it was difficult to infer the optimal duration of therapy from this
meta-analysis. The reduction in septic complications revealed in this study is consistent with the results of other meta-analyses [10,46]. In addition, Chowdhury et al. [9] demonstrated that synbiotics are more effective than probiotics in reducing infection risks and length of hospital stay.

On the whole, probiotics and synbiotics are safe and well tolerated [9,14,47]. Whelan and Myers systematically evaluated the safety issue and adverse effects of probiotics in patients receiving nutritional support [47]. They indicated that in some specific patient groups (e.g. severe acute pancreatitis or liver transplantation), the adverse events may increase after probiotic intervention. Besselink et al. reported that bowel ischemia may occur after probiotic administration in patients with severe acute pancreatitis, although the occurrence was found to be relatively low (6%) [48]. *Lactobacillus* and *S. boulardii*-related sepsis have also been reported in some studies, especially in ICU patients who have inserted central venous catheters (CVCs). However, the researchers indicated that these kinds of infections may also be associated with environmental contamination with the probiotic (for example, *S. boulardii* products may be introduced into CVC lines by unintentional hand contamination) [47]. Thus, the relationship between probiotic products and sepsis in the ICU is weak and requires more evidence. This meta-analysis revealed that synbiotics were better tolerated than probiotics. This is consistent with a recent study by Johnstone et al. that reported that serious adverse events occurred in patients receiving *L. rhamnosus* GG [18].

Due to the variable species of probiotics used in the studies included, it is difficult to evaluate which one was most effective. We performed a subgroup analysis based on probiotics such as *L. rhamnosus* GG, *L. casei*, *L. plantarum* 299 and VSL#3. The analysis showed that the risk of developing VAP was reduced only with VSL#3. Administration of *L. rhamnosus* GG, *L. casei* or *L. plantarum* 299 alone could not reduce the incidence of VAP, mortality, diarrhea, sepsis or other ICU-acquired infections. VSL#3 is a mixture of different bacterial species. The use of a complex mixture of different bacterial species promotes the balance of the microbial composition of the intestines and stomach through the synergistic actions of the different strains. The same may improve microbial dysbiosis in order to lower septic complications in critically ill patients, create a better balance by adding good (probiotic) bacteria to help control the bad bacteria, help to protect and strengthen the intestinal barrier, and prevent bad bacteria from sticking to and irritating the gastrointestinal tract. Therefore, it ultimately reduces the immune response and inflammation caused by the bacteria. However, the same probiotic therapy may have different effects in different patient groups [49].

The results of this meta-analysis are consistent with the proposed theory that the gut is the ‘motor’ of multiple organ dysfunction and the origin of sepsis. Gut motility is often decreased by ischemia, fluid overload and opioids in critically ill patients. Consequently, the mucosal permeability for bacteria and SIRS incidence could increase due to motor stasis and gut intolerance [50]. Montejo [51] found that the complication of intolerance to enteral feeding was significantly increased in critically ill patients. Probiotics and synbiotics alter the gut microbiota and environment to lower septic complications in patients with severe SIRS [12]. Although evidence for the mechanism of probiotic and synbiotic therapy was not provided by this meta-analysis, one of the hypotheses is that the increasing levels of *Lactobacillus* and *Bifidobacterium* lead to increased production of SCFAs in the gut. The gut microbiota and environment maintained by SCFAs that increase the pH in the gut may decrease mucosal permeability and septic complications.

**Limitations of the study**

There are some limitations to this study that need further attention. First, the duration and preparation of probiotics or synbiotic therapy was different among studies included [25,26,28,30,31,41,42]. There were no uniform standards. Second, some studies did not use a placebo to reduce unintentional physical cues and prejudice [14,15,26,35,40,44]. Although there are many published studies regarding the use of probiotics or synbiotics in critically ill adult patients, few of them meet the high-quality standards of evidence-based medicine. Large high-quality multicenter RCTs are needed to reduce heterogeneity and influence.

**Conclusions**

Synbiotics are an effective and safe nutrition therapy that can be used to reduce septic complications in critically ill patients. However, in critically ill patients, administration of probiotics alone compared with placebo resulted in no difference in septic complications. The effect of a mixture of probiotics was better than that of a single probiotic species.

**Abbreviations**

APACHEII scores:Acute Physiology and Chronic Health Evaluation II scores; CI: Confidence interval; CVC: Central venous catheter; GCS:Glasgow Coma Scale; ICU: Intensive care unit; MD: Mean difference; MV:Mechanical ventilation; RCT: Randomized controlled trial; RR: Risk ratio; SCFA: Short-chain fatty acid; SIRS: Systemic inflammatory response syndrome; TBI:Traumatic brain injury; VAP: Ventilator-associated pneumonia.

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**Authors’ contributions**

KW, QZ and HJ performed the study design and conceptualization. KXL, YW, LW, KW and QZ completed the literature retrieval and data extraction. Mathematical modeling and meta-analysis were conducted with the help of KW and MWS. KW and QZ drafted the
manuscript. JZ and HJ contributed to the visualization and edited the final version of the manuscript. All authors approved the manuscript.

Conflicts of Interest
None declared.

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