**SYSTEMATIC REVIEW/META ANALYSIS**

**Probiotics in Critically Ill Patients: An Umbrella Review**

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**Abstract**

**Objectives:** Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host. Because of the widespread usage of antibiotics, acute changes in diet, and the stress of illness, critically ill patients’ homeostasis of the gut microbiome can be disrupted during intensive care unit (ICU) confinement; probiotics are suggested as a beneficial intervention in critically ill patients. We tried to give an overview of the effects of probiotic supplements in critically ill patients based on published systematic reviews (SRs) and meta-analyses (MAs).

**Data sources:** A systematic search was performed in four databases as well as hand searching.

**Study selection:** The results were independently screened in two title/abstracts and full-text stages.

**Data extraction:** Any reported outcomes in each study were extracted, using a data extraction table.

**Data synthesis:** A wide range of outcomes of using probiotic supplements in critically ill patients have been reported in 20 included studies. Based on the current knowledge, we can say that probiotics may reduce the rate of ventilator-associated pneumonia, nosocomial pneumonia, the overall infection rate, duration of mechanical ventilation, and antibiotic use in critically ill patients, but there is not a significant association between using the probiotics and mortality, length of hospitalization, and incidence of diarrhea.

**Conclusion:** Despite the various beneficial effects of probiotics in critically ill patients, there is not yet much evidence supporting the routine use of these supplements and further well-designed multicenter trials are needed to provide “evidence-based” recommendations.

**Keywords:** Critical illness, Intensive care units, Probiotics, Systematic review, Umbrella review.

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**Study Highlights**

- In this umbrella review, we investigated the effects of probiotic supplements in critically ill patients to give an overview of any reported outcome in systematic reviews and meta-analyses.
- Probiotics have been reported to reduce the rate of ventilator-associated pneumonia (VAP), nosocomial pneumonia, the overall infection rate, duration of mechanical ventilation, and antibiotic use in critically ill patients, but they have shown no or a little efficacy in reducing the rate of mortality and length of stay in hospital.
- The low quality of included studies is one of the most common limitations in the included systematic reviews. Our risk of bias assessment results indicated a high level of concerns about methodological misconduct in our included systematic reviews, too.

**Introduction**

Probiotics are nonpathogenic live microorganisms mainly bacteria, yeasts, or fungi, which are effective for the human body's health especially for the digestive system.¹ They can be found in yogurt or other fermented food or supplements. According to the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) definition, probiotics are “Live microorganisms which when administered in adequate amounts confer a health benefit on the host.”² In recent years, the use of these supplements has become popular because of their benefits on human health, especially in infectious diseases, approved in numerous studies.³–⁵ Probiotics contain a variety of microorganisms, but mostly they belong to two groups of bacteria called *Lactobacillus* and *Bifidobacterium*. These supplements help the body maintain its health by replacing “good” bacteria in case of elimination by antibiotics with balancing the number of “good” and “bad” bacteria and also influencing our body’s immune response.⁶ Although probiotics mostly affect the digestive system, they have a broad range of activities affecting other parts of the body, such as skin and urinary tract, too.⁷,⁸

Previously, clinicians’ interest in the microbiome was only limited to the time of occurrence of an infection in the body, but it seems that it is time for a change in this insight. A systematic review (SR) of existing meta-analyses (MAs) performed in 2017 provided a critical overview of the use of probiotic supplements in physiologic and pathological conditions and stated that the evidence-based effects of probiotics were only for antibiotic-associated and *Clostridium difficile*-associated diarrhea and respiratory tract infections, but it also stated a need for further well-conducted studies for ventilator-associated pneumonia (VAP) patients in

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Probiotics in Critically Ill Patients

In 2017, a Cochrane Overviews of Reviews about preventive interventions of probiotics in clinical practice found that whether none of 16 included Cochrane SRs provided high-quality evidence for any outcome, but probiotics decreased the incidence of diarrhea and upper respiratory tract infections, need for antibiotics, and absences from school due to colds and also VAP. Probiotics, with or without a combination of prebiotics, are suggested as a beneficial intervention in critically ill patients. Because of the wide usage of antibiotics, acute changes in diet, and the stress of illness, patients’ homeostasis of the gut microbiome can be disrupted. In this condition, probiotics can sustain the gut microbiota in the patients and prevent opportunistic infections that can live in the absence of protective gut microorganisms. Prevention and treatment of various infections, diarrhea, and perioperative complications in transplant patients are some of the reported benefits of probiotic supplements.

The high level of risk of bias (RoB) in trials makes the existing data inconclusive regarding the routine usage of probiotics in critically ill patients. According to Canadian Critical Care Nutrition Guidelines, the use of probiotics should be considered in critically ill patients, except for an unsafe one, Saccharomyces boulardii. This update was after adding 12 randomized controlled trials (RCTs) conducted from 2009 until 2013. Aggregation of the results of these studies with earlier trials suggested a reduction in VAP with the use of these supplements in critically ill patients. Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) do not recommend the routine use of these supplements in ICU, and the German Society for Nutritional Medicine (DGEM) considers “may” recommendation to be justified. When looking for the best evidence, SRs and MAAs are at the top of the pyramid; so, we are taking to the next level and design this SR of SRs, also called umbrella review, to investigate the effects of probiotic supplements in critically ill patients to give an overview of any reported outcome in SRs and MAAs to reach the most reliable results.

Methods
A systematic search was performed until September 2020 in PubMed, ScienceDirect, EMBASE, and Cochrane database for SRs with (Probiotic OR synbiotic) AND (Critical Care OR Intensive Care Unit OR Critical Ill OR ICU) AND (systematic review OR meta-analysis) keywords and without any filters. Results were imported to EndNote software, and after adding results of hand searching to these records, two authors independently reviewed the identified title/abstracts and full texts in two stages and selected articles which met our eligibility criteria.

The inclusion criteria were as follows: (1) SR journal articles; (2) the population of the study being adult critically ill patients; and (3) the intervention of using probiotics with or without combination with prebiotics. The exclusion criteria were as follows: (1) other types of studies; (2) studies in languages other than English; (3) animal studies; (4) studies of neonates or children; and (5) conference abstracts because of a lack of enough information.

The RoB assessment of studies included in this umbrella review was done by two authors using risk of bias in systematic reviews (ROBIS) tool, which is designed specifically to assess the RoB in SRs. Any disagreement between the researchers is resolved by referring to the corresponding author. ROBIS tool is completed in three phases, and the first phase assesses the relevance of the study which is optional. The second phase of the tool identifies any concerns with the process, including the appreciate eligibility criteria, selection of the studies, data collection and study appraisal, and data synthesis, and finally, the third phase is the judgment of overall RoB in the SR, so this tool assesses the RoB in reviewing process, results, and even conclusion.

The data extraction was done independently by two authors with a data extraction table, including study name, the number of included articles, search databases, interventions and comparisons, quality assessment methods, study population, and outcomes. Flowchart 1 is preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 flow diagram, and detailed information about searching, selecting, and reasons for excluded studies are presented in this flowchart.

Results
The database search resulted in 559 records, and finally, 20 studies were included in umbrella review. A wide range of outcomes of

Flowchart 1: PRISMA flow diagram

| Identification | Records identified through database searching (n = 559) |
|----------------|------------------------------------------------------|
|                | Additional records identified through other sources (n = 24) |
|                | Records after duplicates removed (n = 201) |
|                | Records screened (n = 201) |
|                | Records excluded (n = 162) |
|                | Full-text articles assessed for eligibility (n= 39) |
|                | Full-text articles excluded, with reasons (n = 19) |
|                | • No data about probiotics use in critically ill patients (n = 14) |
|                | • other study designs such as narrative reviews (n = 4) |
|                | • conference abstracts (n = 1) |
|                | Studies included in systematic review (n = 20) |
using probiotic supplements in critically ill patients has been reported in the studies. All the related data about using probiotic supplements in critically ill patients are summarized in Table 1.

### Ventilator-associated Pneumonia

Eleven studies have investigated the relationship between using probiotic supplements and the incidence of VAP. Eight of these studies, including the study with the largest sample size and the latest one, found probiotic supplementation as an effective intervention. Three studies reported the results of the subgroup analysis by the route of administration, and except for one study, the results were still significant when the oral form was excluded. The subgroup of different probiotic regimens in two studies showed a better efficacy for *Lactobacillus rhamnosus* compared to others.

### Incidence of Nosocomial Pneumonia

Four studies assessed the efficacy of probiotic supplements in reducing the incidence of nosocomial pneumonia, and a statistically significant difference was seen in the largest scale study.

### Duration of Mechanical Ventilation

Seven studies reported the results regarding the duration of MV. Until the latest published SR, none of the studies found a significant change with the use of probiotics; but the latest SR, with the largest sample size, found it effective.

### All Infections

There are four SRs giving information in this regard. The last and largest-scale study found that probiotics were effective in reducing the rate of infections.

### Urinary Tract Infection (UTI)

Only one study gave information in this regard. In 2012, a SR with pooling data from two trials found that probiotics were not associated with a decrease in the incidence of UTI as one of their secondary goals.

### Catheter-related Bloodstream Infection (CR-BSI)

Catheter-related bloodstream infection (CR-BSI) was the other outcome reported in two of our included SRs, and none of them found a significant relation.

### Antibiotic Use

Probiotic efficacy in reducing antibiotic use was investigated in two SRs, and the latest one with a larger scale found it good complementation for antibiotic therapy of critically ill patients.

### Antibiotic Use for VAP

Antibiotic use for VAP has been reported in three SRs, with totally different results. Three studies investigated this outcome, and the antibiotic use was not different between placebo and probiotic group in one study, while in the other two ones, antibiotic usage was higher in probiotic and placebo group.

### Septic Complication

None of the three included trials that reported the rate of bacteremia in the MA of Siempos et al. showed any case of bacteremia in the probiotic group. Also, there was no infection or bacteremia due to a probiotic strain used in Barraud et al. SR, based on the results of nine studies.

### Overall Mortality

In 2017, a study of probiotics efficacy in preventing VAP pooled 90-day mortality data of the studies as one of their secondary outcomes. In two studies, supplementation was not associated with a reduction in 90-day mortality. In addition, a 28-day mortality rate was also reported and the difference was not significant. Moreover, there was no significant difference in the overall mortality rate, too.

### Hospital and Intensive Care Unit Mortality

Twelve studies compared the rate of hospital mortality between intervention and control groups but none of them could detect a significant efficacy in this regard. Similar to hospital mortality, 12 studies gave information on ICU mortality. Except for one SR, efficacy was not significant in this regard, too.

### Length of Hospital and Intensive Care Unit Stay

Six different SRs found no changes in the hospital length of stay (LoS) with using probiotics in ICU patients. Thirteen studies investigated ICU LoS as one of their outcomes, and except for two of them, they could not show an effect of probiotics in reducing the length of stay in ICU.

### Diarrhea

Diarrhea was the most common reported adverse event in all studies. Eleven studies compared the rate of diarrhea between probiotic supplement users and the control group but using probiotics was not associated with changes in the rate of diarrhea in any of these studies.

### Safety Issues

In 2010, Whelan et al. investigated 72 different-type studies for assessing the safety of probiotics. Twenty-one studies included in this SR were performed in critically ill patients. Probiotics were tolerated well in most of these studies, and no serious side effects were reported. Also, another SR of the safety of probiotics in evaluated the safety of probiotics in humans and animal models. They found that critically ill patients besides the immune-compromised and postoperative patients are the most at-risk populations to develop adverse effects.

### Others

In 2020, a SR of complementary and alternative medicines’ effect on sleep quality and quantity in adult intensive care patients found no relevant data meeting their inclusion criteria about probiotics; so, to the best of our knowledge, no studies have investigated this outcome.

Probiotics’ potential to modulate the inflammatory process was investigated in a SR in 2019. This study includes only one RCT with a population of critically ill patients showing that probiotics reduce the level of serum interleukin 6 (IL-6) and prolactin (PCT), but also a significant increase in serum protein C levels is observed.

### Risk of Bias Assessment

Results of the RoB assessments are summarized in Table 2 and Figure 1. In terms of eligibility criteria, there was not much concern and most of the studies had low RoB based on our assessment. In the second domain of ROBIS tool, which assesses the RoB in the selection of the studies, the most common concern was about efforts to minimize errors in the selection of the studies. In the data collection and study appraisal domain, most of the studies did not report any try to reduce error in data collection and RoB
| S. No. | Study            | Title                                                                 | Included articles | Search databases                                      | Intervention and comparison | Quality assessment | Population                        | Outcome            | Studies | Patients | Heterogeneity (I²) (%) | Data (95% confidence intervals and p value) |
|-------|------------------|----------------------------------------------------------------------|------------------|------------------------------------------------------|----------------------------|-------------------|-----------------------------------|--------------------|---------|----------|------------------------|------------------------------------------------|
| 1     | Petrof (2012)    | Probiotics in the critically ill: A systematic review of the randomized trial evidence | 23 RCT           | EMBASE, MEDLINE, CINAHL, Cochrane                   | Probiotics compared to a placebo | Own scoring system | Adult (>18 yrs of age) critically ill patients | Infections         | 11      | 981      | 44%                    | RR: 0.82 (0.69 to 0.99; p = 0.03)            |
|       |                  |                                                                      |                  |                                                      |                            |                   |                                    | VAP                | 7       | 1193     | 35%                    | RR: 0.75 (0.59 to 0.97; p = 0.03)            |
|       |                  |                                                                      |                  |                                                      |                            |                   |                                    | Hospital mortality | 14      | 1266     | 0%                     | RR: 0.97 (0.79 to 1.20; p = 0.80)            |
|       |                  |                                                                      |                  |                                                      |                            |                   |                                    | Hospital LoS       | 11      | –        | 69%                    | WMD: −0.68 (−4.46 to 3.11; p = 0.73)          |
|       |                  |                                                                      |                  |                                                      |                            |                   |                                    | ICU mortality      | 6       | 569      | 0%                     | RR: 0.80 (0.59 to 1.09; p = 0.16)           |
|       |                  |                                                                      |                  |                                                      |                            |                   |                                    | ICU LoS            | 12      | –        | 94%                    | WMD: −3.45 (−9.0 to 2.11; p = 0.22)          |
| 2     | Siempos (2010)   | Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials | 5 RCT            | PubMed, Scopus, Current Contents and the Cochrane Central Register of Controlled Trials | Probiotics (or synbiotic) vs control (placebo or other)− excluded articles that referred to pneumonia in critically ill patients in general without specific mention in VAP | Modified Jadad score | Adults undergoing MV | VAP                | 5       | 689      | 39%                    | FEM OR: 0.61 (0.41 to 0.91; p > 0.05)        |
|       |                  |                                                                      |                  |                                                      |                            |                   |                                    |                    |         |          | REM OR: 0.55 (0.31 to 0.98; p > 0.05)        |
| Outcome                        | Studies | Patients | Rate % | FEM OR                  | 95% CI          | p Value | REM OR                  | 95% CI          | p Value |
|-------------------------------|---------|----------|--------|-------------------------|-----------------|---------|-------------------------|-----------------|---------|
| ICU mortality                 | 4       | 481      | 0%     | 0.75 (0.47 to 1.21)     | p > 0.05        |         | 0.76 (0.47 to 1.21)     | p > 0.05        |         |
| Hospital mortality            | 2       | 303      | 0%     | 0.75 (0.46 to 1.24)     | p > 0.05        |         | 0.75 (0.46 to 1.24)     | p > 0.05        |         |
| ICU LoS                       | 3       | 368      | –      | FEM WMD: −0.99 (−1.37 to −0.61) | p > 0.05        |         | REM WMD: −1.93 (−5.82 to 1.95) | p > 0.05        |         |
| Duration of MV                | 3       | 368      | –      | FEM WMD: −0.01 (−0.31 to 0.29) | p > 0.05        |         | REM WMD: −2.24 (−6.65 to 2.16) | p > 0.05        |         |
| Colonization of P. aeruginosa | 2       | 252      | 0%     | FEM OR: 0.35 (0.13 to 0.93) | p > 0.05        |         | REM OR: 0.35 (0.13 to 0.93) | p > 0.05        |         |
| Diarrhea                      | 2       | 324      | 42%    | FEM OR: 0.61 (0.28 to 1.34) | p > 0.05        |         | REM OR: 0.60 (0.13 to 0.93) | p > 0.05        |         |
| Bacteremia                    | 3       | None of the patients |          |                          |                  |         |                          |                  |         |

(Contd...)
### Table 1: (Contd...)

| S. No. | Study | Title                                                                 | Included articles | Search databases                           | Intervention and comparison                                                                 | Quality assessment | Population                                                                 | Outcome                  | Studies | Patients | Heterogeneity (%) | Data (95% confidence interval and p value) |
|--------|-------|----------------------------------------------------------------------|-------------------|--------------------------------------------|------------------------------------------------------------------------------------------------|--------------------|------------------------------------------------------------------------------|--------------------------|---------|----------|-------------------|--------------------------------------------|
| 3      | Gu (2012) | Lack of Efficacy of Probiotics in Preventing Ventilator-Associated Pneumonia | 7 RCT             | PUBMED EMBASE (FILTER: HUMAN, RCT)         | Probiotics compared with a control (placebo or another active agent)—Data available on the incidence of VAP | Jadad scale         | Adult patients undergoing mechanical ventilation                            | VAP                      | 7       | 1142     | 36.9%             | OR: 0.82 (0.55 to 1.24; p = 0.35)          |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | ICU mortality            | 4       | 727      | 0%                  | OR: 0.90 (0.65 to 1.27; p = 0.56)          |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | Hospital mortality       | 4       | 513      | 0%                  | OR: 0.71 (0.48 to 1.07; p = 0.10)          |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | Urinary tract infection  | 2       | 424      | 70%                 | OR: 2.20 (0.50 to 9.71; p = 0.30)          |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | CRBSI                    | 2       | 424      | 70.6%               | OR: 0.51 (0.13 to 2.01; p = 0.33)          |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | Diarrhea                 | 2       | 426      | 0%                  | OR: 1.01 (0.60 to 1.70; p = 0.98)          |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | ICU LoS                  | 4       | 305      | 0%                  | WMD: −0.41 (−3.54 to 2.73; p = 0.80)       |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | Hospital LoS             | 3       | 305      | 0%                  | WMD: −0.99 (−5.36 to 3.38; p = 0.66)       |
|        |       |                                                                        |                   |                                            |                                                                                                |                    |                                                                               | Duration of MV           | 3       | 238      | –                   | WMD: −0.0.10 (−2.36 to 2.16; p = 0.93)     |
### Probiotics in Critically Ill Patients

| Study | Probiotics | RCT | Database | Comparator | Study Design | Outcome | Data Source | Characteristics | Incidence | Odds Ratio (95% CI) | p-Value |
|-------|------------|-----|----------|------------|-------------|---------|-------------|-----------------|-----------|---------------------|---------|
| Bo (2014) | Probiotics for preventing ventilator-associated pneumonia | 8 | MEDLINE and EMBASE | Probiotics (single or mixture of strains, any dosage regimen and any route of administration) with placebo or other controls – Data available on the incidence of VAP | Cochrane criteria | Adult ICU patients (≥ 18 years of age) receiving mechanical ventilation | VAP | 8 | 1018 | 46% | OR: 0.70 (0.52 to 0.95; p = 0.02) |
|         |            |     |          |            |             | ICU mortality | 5 | 703 | 0% | OR: 0.84 (0.58 to 1.22; p = 0.37) |
|         |            |     |          |            |             | Hospital mortality | 4 | 524 | 0% | OR: 0.78 (0.54 to 1.14; p = 0.20) |
|         |            |     |          |            |             | Diarrhea | 4 | 618 | 14% | OR: 0.72 (0.47 to 1.09; p = 0.12) |
|         |            |     |          |            |             | ICU LoS | 4 | 369 | 77% | WMD: -1.6 (−6.53 to 3.33; p = 0.53) |
|         |            |     |          |            |             | Duration of MV | 2 | 203 | 92% | WMD: -6.15 (−18.77 to 6.47; p = 0.34) |
|         |            |     |          |            |             | Systematic antibiotic use | 1 | 259 | – | OR: 1.23 (0.51 to 2.96; p = 0.64) |
|         |            |     |          |            |             | Antibiotic use for VAP | 1 | 138 | – | WMD: -3.00 (−6.04 to 0.04; p = 0.053) |
| Wang (2013) | Probiotics for Preventing Ventilator-Associated Pneumonia: A Systematic Review and Meta-Analysis of High-Quality Randomized Controlled Trials | 5 | WoS, PubMed, Ovid and Cochrane | Comparing probiotics with placebo treatment in – Data available on the incidence of VAP and excluded using selective digestive decontamination-controlled group were | Jadad score | Adult patients undergoing MV | Incidence of VAP | 5 | 844 | – | RR: 0.94 (0.85 to 1.04; p = 0.22) |
|         |            |     |          |            |             | Nosocomial probiotic infection | 6 | 861 | None of the patients. | | |

(Contd...)
Table 1: (Contd...)

| S. No. | Study | Title | Included articles | Search databases | Intervention and comparison | Quality assessment | Population | Outcome | Studies | Patients | Heterogeneity \( I^2 \) | Date (95% confidence interval and p value) |
|--------|-------|-------|-------------------|------------------|----------------------------|-------------------|------------|---------|---------|----------|----------------|---------------------------------|
| 6      | Liu (2012) \cite{2} | Probiotics' effects on the incidence of nosocomial pneumonia in critically ill patients: a systematic review and meta-analysis | 12 RCT PubMed, Cochrane, and EMBASE | Administration of probiotics vs placebo and that reported the incidence of NP or VAP–Probiotics could be administered either alone or in combination with prebiotics | Jadad score | Critically ill patients (admitted to an ICU or having recently undergone abdominal or another major surgical procedure) | Nosocomial pneumonia | 12 | 1546 | 46% | OR = 0.75 (0.57 to 0.97; \( p = 0.03 \)) |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
|        |       |       |                   |                  |                           |                   |            |         |         |          |                |                                 |
| Effect | Study | N | OR  | 95% CI | p  |
|--------|-------|---|-----|--------|----|
| ICU mortality | 3 | 512 | 0% | OR = 0.84 (0.55 to 1.29; p = 0.43) |
| Hospital LoS | 8 | 1110 | 46% | WMD: −0.13 (−0.93 to 0.67; p = 0.75) |
| ICU LoS | 8 | 1093 | 68% | WMD: −0.72 (−1.73 to 0.29; p = 0.16) |
| Diarrhea | 6 | – | 0% | OR = 0.85 (0.58 to 1.26; p = 0.43) |
| Abdominal cramps | 3 | – | 0% | OR = 0.74 (0.47 to 1.17; p = 0.19) |
| ICU-acquired infections | 9 | 1119 | 0% | OR: 0.85 (0.63 to 1.15; p = 0.92) |
| Hospital Mortality | 8 | 841 | 0% | OR: 0.90 (0.65 to 1.23; p = 0.90) |
| ICU-acquired pneumonia | 10 | 1218 | 39% | FEM OR: 0.80 (0.61 to 1.04; p > 0.05) REM OR: 0.53 (0.26 to 1.07 p > 0.05) |

Barraud (2013) compared the administration of probiotics (and/or prebiotics or synbiotics) vs control (placebo or other). Articles must also have reported on ICU or hospital mortality.
Table 1: (Contd…)

| S. No. | Study | Title | Included articles | Search databases | Intervention and comparison | Quality assessment | Population | Outcome | Studies | Patients | Heterogeneity $\hat{\beta}$ | Odds Ratio (95% confidence intervals and p value) |
|--------|-------|-------|-------------------|------------------|----------------------------|-------------------|------------|---------|---------|----------|-------------------|-----------------------------------------------|
|        |       |       |                   |                  | Probiotics alone or associated with prebiotics (synbiotics) compared to a placebo | Own criteria       |            | ICU-acquired CRBSI | 3        | 486     | 62%     | FEM OR: 0.52 (0.30 to 0.87; $p > 0.05$) REM OR: 0.44 (0.17 to 1.13; $p > 0.05$) |
|        |       |       |                   |                  | Probiotics alone or associated with prebiotics (synbiotics) compared to a placebo | Own criteria       |            | Diarrhea | 5        | 648     | –       | OR: 0.72 (0.47 to 1.20; $p > 0.05$) |
|        |       |       |                   |                  | Probiotics alone or associated with prebiotics (synbiotics) compared to a placebo | Own criteria       |            | Duration of MV | 4        | 624     | 81%     | WMD: −0.18 (−1.72 to 1.36; $p > 0.05$) |
|        |       |       |                   |                  | Probiotics alone or associated with prebiotics (synbiotics) compared to a placebo | Own criteria       |            | ICU LoS   | 7        | 802     | 54%     | WMD: −1.49 (−2.12 to −0.87; $p > 0.05$) |
|        |       |       |                   |                  | Probiotics alone or associated with prebiotics (synbiotics) compared to a placebo | Own criteria       |            | Hospital LoS | 6        | 685     | 0%      | WMD: −0.45 (−1.41 to −0.52; $p > 0.05$) |
|        |       |       |                   |                  | Probiotics alone or associated with prebiotics (synbiotics) compared to a placebo | Own criteria       |            | Safety Issues | 9        | –       | –       | There was no infection or bacteremia due to a probiotic strain used, and no studies described the occurrence of ischemic bowel disease. |

8. Manzanares (2016) Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis

Probiotics in Critically Ill Patients
| 9 | Watkinson (2007) | The use of pre-pro- and synbiotics in adult intensive care unit patients: Systematic review | 8 RCT Medline, CINahl, Embase, CENTRAL and the UK National Research Register | Enteral pre-, pro or synbiotic compared with a control | Jadad score | Adult patients admitted to an ICU | Nosocomial infection | 5 | 363 | 78.8% | RR: 1.50 (0.74 to 3.06; p = 0.26) |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  |  | Hospital mortality | 8 | 961 | 0% | RR: 0.96 (0.78 to 1.17; p = 0.66) |
|  |  |  |  |  |  |  | ICU LoS | 3 | 125 | 0% | WMD: 0.03 (−0.04 to 0.05; p = 0.89) |
|  |  |  |  |  |  |  | Nosocomial Pneumonia | 4 | 429 | 0% | RR: 1.40 (0.75 to 2.64; p = 0.29) |

(Contd...)
Table 1: (Contd...)

| S. No. | Study     | Title                                                                 | Included articles | Search databases | Intervention and comparison | Quality assessment | Population | Outcome | Studies | Patients | Heterogeneity ($I^2$) | Data (95% confidence intervals and p value) |
|--------|-----------|----------------------------------------------------------------------|-------------------|------------------|-----------------------------|-------------------|------------|---------|---------|----------|---------------------|------------------------------------------|
| 10     | Brenner (2017) | Growing literature but limited evidence: a systematic review regarding prebiotic and probiotic interventions for those with traumatic brain injury and/or post-traumatic stress disorder | 2 RCT             | OVID MEDLINE, EMBASE, OVID PsycINFO, WoS, CINAHL, and Cochrane Library | – | Taxonomy of Study Design Tool | This SR includes two high RoB studies of ICU patients with traumatic brain injury. In the first study which is performed in China with a sample size of 52 patients, probiotic users were less likely to get infected by more than two types of pathogens ($p = 0.017$), were treated with more types of antibiotics ($p = 0.021$), and had longer stays in the ICU ($p = 0.034$). But Glasgow Coma Scale ($p = 0.68$), receiving MV ($p = 0.77$), Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores in 1,4,8,15 and 21 days, duration of antibiotic use ($p = 0.15$) and 28-day mortality ($p = 0.70$) were not significantly affected. In the second study performed in Brazil, 20 participants with brain injury were divided into two groups of an early enteral diet or glutamine and probiotics added to the diet. Based on their results, using probiotics was associated with a reduction in infection rate ($p = 0.03$), the number of infections per patient ($p < 0.01$), ICU stay ($p < 0.01$), and days of mechanical ventilation ($p = 0.04$). |
| 11     | Chen (2018) | Probiotics are effective in decreasing the incidence of ventilator-associated pneumonia in adult patients: a meta-analysis of randomized controlled trials | 10 RCT | PubMed and WoS | A comparison of probiotics with placebo or other drugs | Cochrane Criteria Adult critically ill participants (≥18 years) | VAP | 10 | 1403 | 32% | FEM OR: 0.69 (0.54 to 0.88; $p = 0.003$) |
|        |           |                                                                       |                   |                  |                             |                   | ICU mortality | 6  | 938  | 0%  | FEM OR: 0.95 (0.67 to 1.33; $p = 0.76$) |
|        |           |                                                                       |                   |                  |                             |                   | Hospital mortality | 5 | 759 | 0% | FEM OR: 0.86 (0.62 to 1.18; $p = 0.35$) |
|        |           |                                                                       |                   |                  |                             |                   | Diarrhea | 4 | 618 | 14% | FEM OR: 0.72 (0.49 to 1.09; $p = 0.12$) |
|        |           |                                                                       |                   |                  |                             |                   | ICU stay | 4 | 432 | 79% | REM WMD: −1.74 (−6.74 to 3.27; $p = 0.50$) |
| Study | Year | Title | Number of RCTs | Database(s) | Intervention | Patient Population | Summary |
|-------|------|-------|----------------|-------------|--------------|-------------------|---------|
| Cooke (2020) | 2020 | Effectiveness of complementary and alternative medicine interventions for sleep quality in adult intensive care patients: A systematic review | 17 | Medline (EBSCO host), CINAHL, PsycINFO, Cochrane library and Scopus | Complementary and alternative medicine interventions | Adult ICU patients | Authors didn’t find any article about the effects of probiotics that met their incursion criteria. |
| Didari (2014) | 2014 | A systematic review of the safety of probiotics | 13 | PubMed, WoS, Google Scholar and Scopus | Probiotic use | Adult patients in ICU | Out of 13 of their included studies involving ICU patients, one RCT reported a few adverse events and bowel distension was reported in one case series study. Finally, in a study in critically ill adults with severe acute pancreatitis an increase in mortality and bowel ischemia was reported with the use of a multispecies probiotic product (Ecologic 641). |
| Fan (2019) | 2019 | Synbiotics for prevention of ventilator-associated pneumonia: a probiotics strain-specific network meta-analysis | 14 | PubMed, WoS, EMBASE, and Cochrane databases | Probiotics, either alone or in combination with other interventions; Cochrane Handbook for Systematic Reviews | Patients who underwent mechanical ventilation VAP | Probiotics, either alone or in combination with other interventions; Cochrane Handbook for Systematic Reviews | Patients who underwent mechanical ventilation VAP |

### Table

| Outcome | N | % | REM WMD: |
|---------|---|---|-----------|
| Duration of MV | 2 | 215 | 93% | -6.21 (-18.83 to 6.41; p = 0.34) |
| Days of antibiotics for VAP | 2 | 381 | 31% | -1.48 (-2.90 to -0.07; p = 0.04) |
| Hospital mortality | 8 | 1114 | 0% | OR: 0.69 (0.55 to 0.88; p = 0.002) |
| ICU mortality | 9 | 1322 | 0% | OR: 0.89 (0.67 to 1.17; p = 0.39) |
| ICU LoS | 5 | 538 | 83% | WMD: -2.40 (-6.75 to 1.95; p = 0.28) |
| Diarrhea | 6 | 1003 | 34% | OR: 0.75 (0.51 to 1.10; p = 0.14) |

(Contd...)
| S. No. | Study | Title | Included articles | Search databases | Intervention and comparison | Quality assessment | Population | Outcome | Studies | Patients | Heterogeneity (I²) | Data (95% confidence intervals and p value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | Maia (2019)<sup>3</sup> | Effects of probiotic therapy on serum inflammatory markers: A systematic review and meta-analysis | 58 (1 in ICU) | PubMed/ MEDLINE, EMBASE and Cochrane Library | Probiotic therapy vs control | Jadad | Critically ill | There was a significant decrease in serum IL-6 levels (from 211.85 ± 112.76 to 71.80 ± 28.41) (p < 0.001) and PCT levels (from 1.67 ± 1.27 to 0.47 ± 0.41) (p < 0.001) and a significant increase in serum protein C levels (from 7.47 ± 3.61 to 12.87 ± 3.63) (p < 0.001) in probiotic group during the study. | | |
| 16 | Whelan (2010)<sup>30</sup> | Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials | 72 Studies (21 in ICU) | MEDLINE, EMBASE, CINAHL, CENTRAL, Nutrition and Food Sciences, WoS | Patients receiving nutritional support | – | Adults in ICU | Only in one study a few side effects were reported and two patients in one study developed bowel distention. One trial reported few side effects, 11 studies reported no adverse events and 8 studies gave no information about safety. | | |
| 17 | Roquilly (2014)<sup>59</sup> | Pneumonia prevention to decrease mortality in intensive care unit: A systematic review and meta-analysis | 157 RCT (13 RCT) | MEDLINE and COCHRANE | Probiotic/ Symbiotic Criteria | Cochrane | Critically ill adult patients hospitalized in ICU and evaluating digestive prophylactic methods | Hospital mortality | 13 | 1569 | 23% | RR: 0.89 (0.66 to 1.18; p = 0.41) |
| | | | | | | | | Hospital-acquired pneumonia | 12 | 1585 | 42% | RR: 0.76 (0.66 to 1.03; p = 0.07) |
| | | | | | | | | Duration of MV | 5 | 899 | 0% | WMD: −0.12 (−1.03 to 0.79; p = 0.79) |
| | | | | | | | | ICU LoS | 9 | 1275 | 46% | WMD: −1.08 (−2.19 to 0.03; p = 0.06) |
|   | Probiotics in Critically Ill Patients |
|---|-------------------------------------|
| 18 | Probiotics for the Prevention of Ventilator-Associated Pneumonia: A Meta-Analysis of Randomized Controlled Trials |
|   | PubMed, EMBASE, and Cochrane databases |
|   | Compared probiotics with placebo or standard therapy |
|   | Cochrane Criteria |
|   | Adults receiving mechanical ventilation |
|   | VAP |
|   | ICU mortality |
|   | ICU LoS |
|   | ICU LoS (sensitively analysis) |
|   | Duration of MV |
|   | Duration of MV (sensitively analysis) |
|   | Antibiotic use for VAP |
|   | Diarrhea |
| 14 RCTs | 14 |
| REM OR: | 0.62 (0.45 to 0.85; p = 0.003) |
| REM OR: | 0.95 (0.67–1.34; p = 0.77) |
| REM MDW: | –1.19 (–4.74 to 2.15; p > 0.05) |
| REM MDW: | –0.77 (–2.58 to 1.04; p = 0.40) |
| REM MDW: | –2.37 (–4.67 to –0.08; p < 0.05) |
| REM MDW: | –0.91 (–2.20 to 0.38; p = 0.17) |
| REM MDW: | –1.44 (–2.88 to –0.01; p > 0.05) |
| REM OR: | 0.72 (0.45 to 1.15; p > 0.05) |
|   | (Contd...)
Table 1: (Contd…)

| S. No. | Study         | Title                                                                 | Included articles | Search databases          | Intervention and comparison | Quality assessment | Population                | Outcome      | Studies | Patients | Heterogeneity $I^2$ | Data (95% confidence intervals and p value) |
|--------|---------------|----------------------------------------------------------------------|------------------|---------------------------|------------------------------|-------------------|---------------------------|--------------|---------|----------|-----------------------|-------------------------------------------|
| 20     | Weng (2017)²⁹ | Probiotics for Preventing Ventilator-associated Pneumonia in Mechanically Ventilated Patients: A Meta-analysis with Trial Sequential Analysis | 13 RCT           | PubMed, Embase, and CENTRAL | Comparing probiotics with control | Cochrane Criteria | Mechanically ventilated patients | VAP          | 13      | 1969     | 40%                   | RR: 0.73 (0.60 to 0.89; p = 0.002)        |
|        |               |                                                                      |                  |                           |                              |                   |                           | VAP (Sensitivity analysis) | 10      | –       | –        | REM RR = 0.86 (0.66 to 0.97; p = 0.02) |
|        |               |                                                                      |                  |                           |                              |                   |                           | 90-day mortality          | 2       | 317     | 0%       | REM RR = 1.00 (0.72 to 1.37; p = 0.99) |
|        |               |                                                                      |                  |                           |                              |                   |                           | Overall mortality         | 9       | 1296    | 0%       | FEM RR: 0.84 (0.70 to 1.02; p = 0.09)   |
|        |               |                                                                      |                  |                           |                              |                   |                           | Overall mortality (Sensitivity analysis) | 7       | –       | –        | RR = 0.86 (0.70 to 1.07; p = 0.17)      |
|        |               |                                                                      |                  |                           |                              |                   |                           | 28-Day mortality          | 2       | 317     | 0%       | FEM RR: 1.06 (0.72 to 1.57; p = 0.99)   |
|        |               |                                                                      |                  |                           |                              |                   |                           | ICU mortality             | 6       | 938     | 0%       | FEM RR: 0.97 (0.74 to 1.27; p = 0.82)   |
|        |               |                                                                      |                  |                           |                              |                   |                           | ICU mortality (Sensitivity analysis) | 5       | –       | –        | RR = 0.96 (0.73 to 1.26; p = 0.78)      |
|        |               |                                                                      |                  |                           |                              |                   |                           | Hospital mortality        | 6       | 877     | 0%       | FEM RR = 0.81 (0.73 to 1.26; p = 0.78)   |
|        |               |                                                                      |                  |                           |                              |                   |                           | Hospital mortality (Sensitivity analysis) | 4       | –       | –        | RR = 0.83 (0.73 to 1.26; p = 0.78)      |
| Condition             | Study | Patients | % Controlled | FEM RR/REM MD |
|-----------------------|-------|----------|--------------|---------------|
| Diarrhea              | 5     | 768      | 0%           | FEM RR 0.99 (0.83 to 1.19; p = 0.92) |
| ICU LoS               | 5     | 538      | 83%          | REM MD = -2.40 (-6.75 to 1.95; p = 0.28) |
| ICU LoS (Sensitivity analysis) | 3     | -        | -            | MD = -3.88 (-10.51 to 2.76; p = 0.25) |
| Hospital LoS          | 4     | 682      | 79%          | REM MD = -1.34 (-6.21 to 3.54; p = 0.59) |
| Hospital LoS (Sensitivity analysis) | 3     | -        | -            | MD = 1.47 (-6.21 to 3.54; p = 0.59) |
| Duration of MV        | 4     | 512      | 83%          | REM MD = -3.32 (-6.21 to 3.54; p = 0.59) |
| Duration of MV (Sensitivity analysis) | 3     | -        | -            | MD = -3.32 (-6.21 to 3.54; p = 0.59) |

RCT, randomized controlled trial; VAP, ventilator-associated pneumonia; LoS, length of stay; ICU, intensive care unit; MV, mechanical ventilation; RR, relative risk; OR, odds ratio; WMD, weighted mean difference; MD, mean difference; WoS, web of science; IL-6, interleukin 6; FEM, fixed-effect model; REM, random-effects model
| Study                     | Domain 1: Study eligibility criteria | Domain 2: Identification and selection of studies | Domain 3: Data collection and study appraisal | Domain 4: Synthesis and findings | Phase 3: Judging risk of bias in the review process |
|--------------------------|-------------------------------------|--------------------------------------------------|--------------------------------------------|--------------------------------|---------------------------------|
|                          | Q1  Q2  Q3  Q4  Q5  Overall         | Q1  Q2  Q3  Q4  Q5  Overall                     | Q1  Q2  Q3  Q4  Q5  Overall             | Q1  Q2  Q3  Q4  Q5  Overall | Qa  Qb  Qc  Overall            |
| Petrof et al. (2012)     | Y    Y    Y    Y    Y    LOW             | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW             | Y    Y    Y    Y    Y    LOW             | N    PY    Y    HIGH          |
| Siempos et al. (2010)    | Y    N    Y    Y    Y    HIGH           | Y    Y    Y    Y    Y    HIGH                | Y    Y    Y    Y    Y    PN             | Y    Y    Y    Y    Y    HIGH             | N    Y    Y    HIGH          |
| Gu et al. (2012)         | Y    Y    PY    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    PN             | Y    Y    Y    Y    Y    HIGH             | N    Y    Y    HIGH          |
| Bo et al. (2015)         | Y    Y    Y    Y    Y    Y    LOW       | Y    Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    Y              | Y    Y    Y    Y    Y    LOW             | Y    Y    Y    LOW           |
| Wang et al. (2013)       | Y    Y    y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    Y              | Y    Y    Y    Y    Y    LOW             | Y    Y    Y    LOW           |
| Liu et al. (2012)        | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Barraud et al. (2013)    | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Manzanares et al. (2016) | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    PN             | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Watkinson et al. (2007)  | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    N              | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Brenner et al. (2017)    | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | Y    Y    Y    LOW           |
| Chen et al. (2018)       | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Cooke et al. (2020)      | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Didari et al. (2014)     | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Fan et al. (2019)        | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| Maia et al. (2019)       | Y    Y    y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | Y    Y    Y    LOW           |
| Whelan et al. (2018)     | Y    Y    N    Y    Y    HIGH           | Y    Y    N    Y    Y    HIGH                | Y    Y    N    Y    Y    HIGH           | Y    Y    N    Y    Y    HIGH             | N    Y    Y    HIGH          |
| Roquilly et al. (2014)   | Y    Y    N    Y    Y    HIGH           | Y    Y    N    Y    Y    HIGH                | Y    Y    N    Y    Y    HIGH           | Y    Y    N    Y    Y    HIGH             | N    Y    Y    HIGH          |
| Su et al. (2020)         | Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |
| van Ruissen et al. (2019)| Y    Y    Y    Y    Y    LOW            | Y    Y    Y    Y    Y    LOW                | Y    Y    Y    Y    Y    LOW           | Y    Y    Y    Y    Y    LOW             | N    Y    Y    HIGH          |

Y, yes; PY, probably yes; PN, probably no; N, no; NI, no information
assessment. Except for three studies, others assessed the RoB in their included studies, with Jadad score, Cochrane criteria, or other quality assessment tools. Finally, in terms of data synthesis biases, the similarity of pooled data was not considered in most of the studies. Also, the authors did not address the RoB assessment results in their final data synthesis, in about half of the studies. Overall, RoB assessment results indicated a high level of concerns about methodological misconduct in our included SRs.

**Discussion**

In this overview of SRs, all the reported outcomes regarding probiotic supplements were investigated. There are still a lot of controversies between different studies, which make it impossible to reach a reliable conclusion. Based on the current knowledge, we can say that probiotics may reduce the rate of VAP, nosocomial pneumonia, the overall infection rate, duration of mechanical ventilation, and antibiotic use in critically ill patients, but it has no or little efficacy in reducing the rate of mortality and length of hospitalization. In addition, there is not a significant association between using probiotics and the incidence of diarrhea.

Infection during ICU confinement is a worldwide challenge with a high mortality rate reaching about 60%. VAP is the second most common nosocomial infection in the United States, after catheter-associated urinary tract infections. It imposes a great financial burden on the healthcare system. The American Thoracic Society recommended the antibiotics for treatment of VAP in ICU patients, but the increasing concern of multidrug-resistant bacteria highlighted the importance of prevention strategies. A study comparing different interventions found probiotic a cost-effective intervention, in the prevention of VAP. Despite the possible efficacy of probiotic supplements in the treatment of VAP, its efficacy in the prevention of death is not considerable. It could be because of the limited attribution of VAP in the mortality of ICU patients. In other words, probiotics could not affect the other more prevalent critical illness of ICU patients, such as organ failure, and consequently could not significantly reduce the mortality rate.

The safety of probiotic supplements is not something worrying for many people. It has been used in foods and dairy products for a long time, and many people consider it a safe product. As many probiotics are sold as dietary supplements in the United States (US), it does not require FDA approval, so there is a lack of certain information on the safety of these supplements. In 2019, FDA stated that “Over-the-counter probiotics used in clinical trials to investigate their potential use for various disease conditions require more stringent quality controls to ensure purity and potency of the product.” Also, the US National Institutes of Health (NIH) believes that the risk of harmful effects of living microbiota is greater for critically ill patients. In 2011, a review of 622 studies found a lack of assessment and systematic reporting of adverse events in probiotic intervention studies and the safety of probiotic interventions was still unclear. In 2018, a SR of 384 probiotic, prebiotic, and synbiotic trials found that the broad conclusion of the safety of these supplements without reporting safety data is impossible. In this study, 53 trials involved hospitalized or critical care patients, and 37 of them included harm-related data in the publication. Studies also reported that probiotics might lead to fungemia and bacteremia and it should be used with caution in immune-compromised patients and older adults.

A Cochrane review of pharmacological interventions for acute pancreatitis in 2017 investigated the length of ICU stay in pancreatitis patients. None of 13 studies (n = 1,188) reported a consistent decrease in length of ICU stay. Also, a MA of RCTs in 2013 investigated the efficacy of pre-, pro-, or synbiotic supplements in trauma patients. According to this study’s results, use of these supplements reduced the length of ICU stay (two trials; SMD, −0.71; 95% CI, −1.09 to −0.34, p <0.001), incidence of nosocomial infections (five trials; RR, 0.65; 95% CI, 0.45–0.94, p = 0.02), and VAP (three trials; RR, 0.59; 95% CI, 0.42–0.81, p = 0.001) in these patients, but no reduction in mortality (four trials; RR, 0.63; 95% CI, 0.32–1.26, p = 0.19) was reported in this study.
did not meet our inclusion criteria because of their different study population.

This umbrella review indicates the need for more well-designed clinical trials rather than SRs. The restoration of gut microflora in critical illness trial (ROCIT) is one of the future studies. This Australian multicenter study can provide clear evidence about probiotic usage in ICU patients in a large sample size. The low quality of included studies is one of the most common limitations in the included SRs, which should be considered in future studies. Also, publication bias is one of the other concerns. The heterogeneity in different species was the common bias, which can harm the validity of the findings. This could raise from the limited published studies, which force the authors to pool heterogenic data to reach a single outcome. Different critically ill definitions and various diagnostic criteria for VAP are the other limitations, which should not be neglected. The different diagnostic criteria not only can result in great variation in the incidence of VAP but also can influence the mortality rate. The main strength of our study was the novel study protocol to assess the efficacy of probiotic supplements in critically ill patients based on the best available evidence. Also, adding other resources to search results of four databases led to the full coverage of published studies. Using a standard approach in conducting this review is the other strength of this study.

**Conclusion**

In conclusion, despite the various beneficial effects of probiotics in critically ill patients, there is not yet much evidence supporting their routine use and the available evidence is not sufficient enough to recommend the use of probiotics in critically ill patients. Further well-designed multicenter trials are needed to confirm their effects and benefits in these patients and to provide “evidence-based” recommendations.

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