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 wide 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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intensive care unit (ICU).[9] 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.[10] 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.[11] In this condition, probiotics can sustain the gut microbiota in the patients[12] and prevent opportunistic infections that can live in the absence of protective gut microorganisms.[13] Prevention and treatment of various infections, diarrhea, and perioperative complications in transplant patients[14] 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.[15,16] 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.[17] 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,[18] and the German Society for Nutritional Medicine (DGEM) considers "may" recommendation to be justified.[19] When looking for the best evidence, SRs and MAs 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 MAs 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.

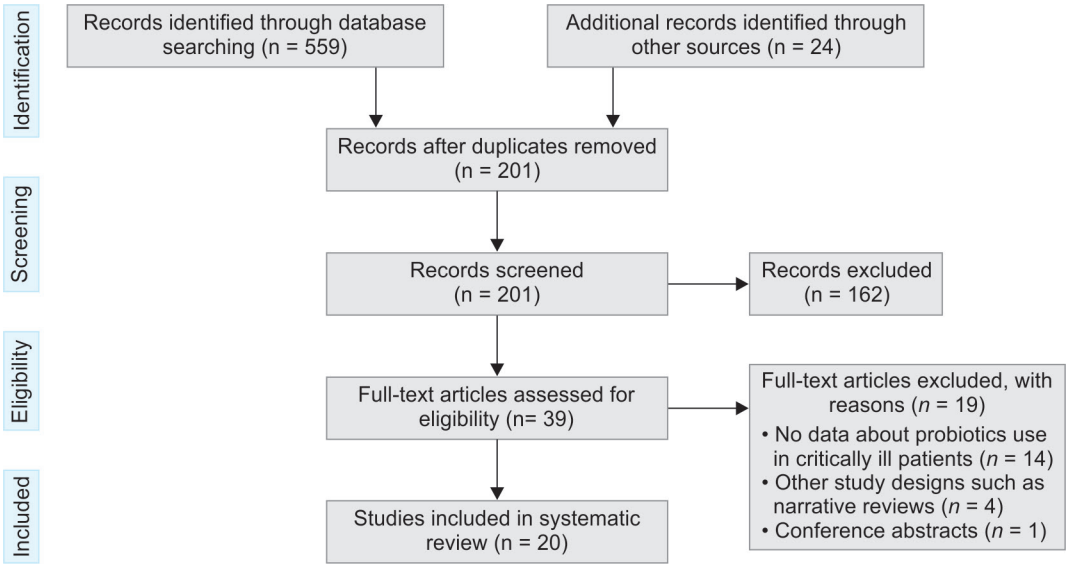
The RoB assessment of studies included in this umbrella review was done by two authors using risk of bias in systematic reviews (ROBIS) tool, which is designed specifically to assess the RoB in SRs. Any disagreement between the researchers is resolved by referring to the corresponding author. ROBIS tool 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.[20]

The data extraction was done independently by two authors with a data extraction table, including studies 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,[21] 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



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[22] and the latest one,[23] found probiotic supplementation as an effective intervention. Three studies[24–26] 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[22,26] 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.[27]

Duration of Mechanical Ventilation

Seven studies reported the results regarding the duration of MV. Until the latest published SR,[23] 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[28] 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[25] 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[28] 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.[24] 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.[27] SR, based on the results of nine studies.

Overall Mortality

In 2017, a study of probiotics efficacy in preventing VAP[29] 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,[13] 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,[24,27] 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.[30] 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 2014[31] 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.[32]

Probiotics' potential to modulate the inflammatory process was investigated in a SR in 2019.[33] This study includes only one RCT with a population of critically ill patients[34] 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

Table 1: Summary of the findings of the included studies

								Outcome				
S. No.	*Study*	*Title*	*Included articles*	*Search databases*	*Intervention and comparison*	*Quality assessment*	*Population*	*Outcome*	*Studies*	*Patients*	*Hetero-geneity (I^2)*	*Data (95% confidence intervals and p value)*
1	Petrof (2012)[13]	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; $p = 0.22$)
								Diarrhea	12	–	5%	RR: 0.95 (0.80 to 1.13; $p = 0.54$)
2	Siempos (2010)[24]	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; $p > 0.05$)

ICU mortality	4	481	0%,	FEM OR: 0.75 (0.47 to 1.21; $p > 0.05$) REM OR: 0.76 (0.47 to 1.21; $p > 0.05$)
Hospital mortality	2	303	0%	FEM OR: 0.75 (0.46 to 1.24; $p > 0.05$) REM OR: 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		

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Table 1: *(Contd...)*

								Outcome				
S. No.	*Study*	*Title*	*Included articles*	*Search databases*	*Intervention and comparison*	*Quality assessment*	*Population*	*Outcome*	*Studies*	*Patients*	*Hetero-geneity (I^2)*	*Data (95% confidence intervals and p value)*
3	Gu (2012)[25]	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	36.5%	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; $p = 0.93$)

4	Bo (2014)[26]	Probiotics for preventing ventilator-associated pneumonia	8 RCT	CENTRAL 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; $p = 0.053$)
								Nosocomial probiotic infection	6	861	None of the patients.	
5	Wang (2013)[52]	Probiotics for preventing ventilator-associated pneumonia: a systematic review and meta-analysis of high-quality randomized controlled trials	5 RCT	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; $p = 0.22$)

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Table 1: *(Contd...)*

								Outcome				
S. No.	*Study*	*Title*	*Included articles*	*Search databases*	*Intervention and comparison*	*Quality assessment*	*Population*	*Outcome*	*Studies*	*Patients*	*Hetero-geneity (I^2)*	*Data (95% confidence intervals and p value)*
								Hospital mortality	4	636	0%	RR: 0.81 (0.62 to 1.06; $p = 0.13$)
								ICU mortality	3	491	3.1%	RR: 0.84 (0.61 to 1.16; $p = 0.29$)
								Length of stay in ICU	3	365	Q= 6.01	ES: −3.22 (−9.14 to −2.70; $p = 0.29$)
								Etiology of the infections	3	118	G+ bacterial infection RR: 1.21 (0.83 to 1.75; $p = 0.33$) G- bacterial infection RR: 0.87 (0.67 to 1.13; $p = 0.30$) *Pseudomonas aeruginosa* RR: 0.36 (0.11 to 0.91; $p = 0.03$)	
6	Liu (2012)[53]	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; $p = 0.03$)
								VAP			54%	OR = 0.68 (0.42 to 1.11; $p = 0.12$)
								Nosocomial pneumonia in surgical critically ill patients			41%	OR: 0.67 (0.45 to 1.01; $P = 0.05$)
								Hospital mortality	9	1058	51%	OR = 0.93 (0.50 to 1.74; $p = 0.82$)

								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; $p = 0.19$)
7	Barraud (2013)[27]	Impact of the adminis-tration of probiotics on mortality in critically ill adult patients	13 RCT	PubMed, Scopus, and the Cochrane Central Register for Controlled Trials	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	Jadad score	Critically ill adult patients admitted to the ICU	ICU mortality	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 infections	9	969	80%	FEM OR: 0.80 (0.61 to 1.04; $p > 0.05$) REM OR: 0.53 (0.26 to 1.07 $p > 0.05$)
								Antibiotics consumption	–	–	0%	FEM WMD: −1.67; −3.62 to 0.28; $p = 0.48$)
								ICU-acquired pneumonia	10	1218	39%	FEM OR: 0.58 (0.42 to 0.79; $p > 0.05$) REM OR: 0.54 (0.35 to 0.84; $p > 0.05$)

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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)
								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; $p > 0.05$)
								Diarrhea	5	648	–	OR: 0.72 (0.47 to 1.10; $p > 0.05$)
								Duration of MV	4	624	81%	WMD: −0.18 (−1.72 to 1.36; $p > 0.05$)
								ICU LoS	7	802	54%	WMD: −1.49 (−2.12 to −0.87; $p > 0.05$)
								Hospital LoS	6	685	0%	WMD: −0.45 (−1.41 to 0.52; $p > 0.05$)
								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)[28]	Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis	30 RCT	MEDLINE, Embase, CINAHL, Cochrane	Probiotics alone or associated with prebiotics (synbiotics) compared to a placebo	Own criteria	Adult (≥18 years of age) critically ill patients—*If the study population was unclear, a mortality rate higher than 5% in the control group considered as critically ill*	New infections	14	1233	36%	RR: 0.80 (0.68 to 0.95; $p = 0.009$)
								VAP	9	1326	19%	RR: 0.74 (0.61 to 0.90; $p = 0.002$)

								Hospital mortality	17	1638	0%	RR: 0.98 (0.82 to 1.18; $p = 0.85$)
								ICU LoS	14	–	93%	WMD: −3.26 (−7.82 to 1.31; $p = 0.16$)
								Hospital LoS	9	–	74%	WMD: −0.58 (−3.66 to 2.50; $p = 0.71$)
								Diarrhea	9	1259	5%	RR: 0.97 (0.82 to 1.15; $p = 0.74$)
								Antibiotic days	4	470	32%	WMD: −1.12 (−1.72 to −0.51, $p = 0.0003$)
9	Watkinson (2007)[54]	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 (−0.44 to 0.51; $P = 0.89$)
								Nosocomial pneumonia	4	429	0%	RR:1.40 (0.75 to 2.64; $p = 0.29$)

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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)[57]	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[55] 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,[56] 20 participants with brain injury were dived 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)[50]	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; $p = 0.50$)

								Duration of MV	2	215	93%	REM WMD: −6.21 (−18.83 to 6.41; $p = 0.34$)
								Days of antibiotics for VAP	2	381	31%	REM WMD: −1.48 (−2.90 to –0.07; $p = 0.04$)
12	Cooke (2020)[32]	Effectiveness of complementary and alternative medicine interventions for sleep quality in adult intensive care patients: A systematic review	17 RCT	Medline (EBSCO Host), CINAHL, PsychINFO, Cochrane library and Scopus	Complementary and alternative medicine interventions	Cochrane criteria	Adult ICU patients	Authors didn't find any article about the effects of probiotics that met their incursion criteria.				
13	Didari (2014)[31]	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).				
14	Fan (2019)[22]	Synbiotics for prevention of ventilator-associated pneumonia: a probiotics strain-specific network meta-analysis	14 RCT	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	14	2044	17%	OR: 0.69 (0.55 to 0.88; $p = 0.002$)
								Hospital mortality	8	1114	0%	OR: 0.81 (0.61 to 1.06; $p = 0.13$)
								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...)

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)
15	Maia (2019)[33]	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)[30]	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)[58]	Pneumonia prevention to decrease mortality in intensive care unit. A systematic review and meta-analysis	157 RCT (13 RCT)	MEDLINE and COCHRANE	Probiotic/ Symbiotic	Cochrane criteria	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; $p = 0.06$)

18	Su (2020)[23]	Probiotics for the prevention of ventilator-associated pneumonia: A meta-analysis of randomized controlled trials	14 RCTs	PubMed, EMBASE, and Cochrane databases	Compared probiotics with placebo or standard therapy	Cochrane criteria	Adults receiving mechanical ventilation	VAP	14	1575	43%	REM OR: 0.62 (0.45 to 0.85; $p = 0.003$)
								ICU mortality	6	993	0%	REM OR: 0.95 (0.67–1.34; $p = 0.77$)
								ICU LoS	10	1,418	89%	REM MDW: –1.29 (–4.74 to 2.15; $p > 0.05$)
								ICU LoS (sensitivity analysis)	7	1103	43%	REM MDW: –0.77 (–2.58 to 1.04; $p = 0.40$)
								Duration of MV	8	1,197	78%	REM MDW: –2.37 (–4.67 to –0.08; $p > 0.05$)
								Duration of MV (sensitivity) analysis	6	897	25%	REM MDW: –0.91 (–2.20 to 0.38; $p = 0.17$)
								Antibiotic use for VAP	2	373	41%	REM MDW: –1.44 (–2.88 to –0.01; $p > 0.05$)
								Diarrhea	6	861	30%	REM OR: 0.72 (0.45 to 1.15; $p > 0.05$)
19	van Ruissen (2019)[59]	Manipulation of the microbiome in critical illness probiotics as a preventive measure against ventilator-associated pneumonia	8 RCTs	MEDLINE via PubMed and WoS	Excluded if probiotics were used in combination with a prebiotic or an antimicrobial agent	Cochrane criteria	Patients were over 18 years of age, admitted to an ICU and receiving invasive ventilation	Incidences of VAP	*The incidence of VAP ranged from 4 to 36% in the intervention groups and from 13 to 50% in the control groups. The relative risk for VAP ranged between 0.30 and 1.41. Three trials showed a significant difference in favor of probiotic therapy between the intervention and the control groups. The incidence of VAP episodes ranged from 13 to 30 per 1000 ventilation days. One trial reported diarrhea as a side effect of the intervention. The other six trials did not report on the side effects of the intervention.*				

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Table 1: *(Contd...)*

								Outcome				
S. No.	*Study*	*Title*	*Included articles*	*Search databases*	*Intervention and comparison*	*Quality assessment*	*Population*	*Outcome*	*Studies*	*Patients*	*Hetero-geneity (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%	FEM 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; $p = 0.78$)

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

Table 2: Risk of bias in the included studies

		Phase 2: Identifying concerns with the review process																								*Phase 3: Judging risk of bias*			
		Domain 1: Study eligibility criteria						*Domain 2: Identification and selection of studies*						*Domain 3: Data collection and study appraisal*						*Domain 4: Synthesis and findings*							*Risk of bias in the review*			
Study		*Q1*	*Q2*	*Q3*	*Q4*	*Q5*	*Overall*	*Q1*	*Q2*	*Q3*	*Q4*	*Q5*	*Overall*	*Q1*	*Q2*	*Q3*	*Q4*	*Q5*	*Overall*	*Q1*	*Q2*	*Q3*	*Q4*	*Q4*	*Q5*	*Overall*	*Qa*	*Qb*	*Qc*	*Overall*
1	Petrof et al. (2012)	Y	Y	Y	Y	Y	LOW	PY	Y	Y	Y	Y	LOW	PN	Y	PY	PY	Y	HIGH	Y	Y	N	Y	Y	N	HIGH	N	PY	Y	HIGH
2	Siempos et al. (2010)	Y	N	Y	Y	Y	HIGH	Y	Y	PN	Y	Y	HIGH	Y	Y	Y	Y	PN	HIGH	Y	Y	Y	Y	N	N	HIGH	N	Y	Y	HIGH
3	Gu et al. (2012)	Y	Y	PY	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	PN	HIGH	Y	Y	N	Y	Y	Y	HIGH	N	Y	Y	HIGH
4	Bo et al. (2015)	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	Y	LOW	Y	Y	Y	LOW
5	Wang 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	Y	LOW	Y	Y	Y	LOW
6	Liu et al. (2012)	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	N	Y	Y	Y	HIGH	N	Y	Y	HIGH
7	Barraud et al. (2013)	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	PN	HIGH	Y	Y	N	Y	N	N	HIGH	N	Y	Y	HIGH
8	Manzanares et al. (2016)	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	PN	HIGH	PN	Y	Y	PY	Y	HIGH	Y	Y	Y	Y	Y	Y	LOW	N	Y	Y	HIGH
9	Watkinson et al. (2007)	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	N	HIGH	Y	Y	Y	Y	PN	HIGH	Y	Y	N	Y	N	N	HIGH	N	Y	Y	HIGH
10	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	Y	LOW	Y	Y	Y	LOW
11	Chen et al. (2018)	Y	Y	Y	Y	Y	LOW	N	Y	Y	Y	Y	HIGH	PN	Y	Y	Y	PN	HIGH	Y	Y	N	Y	N	N	HIGH	N	Y	Y	HIGH
12	Cooke et al. (2020)	Y	Y	Y	Y	Y	LOW	Y	PN	Y	Y	N	HIGH	PN	Y	Y	Y	Y	HIGH	Y	Y	Y	Y	Y	Y	LOW	N	Y	Y	HIGH
13	Didari et al. (2014)	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	PN	HIGH	PN	Y	Y	N	N	HIGH	Y	Y	Y	Y	Y	Y	LOW	N	Y	Y	HIGH
14	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	Y	LOW	Y	Y	Y	LOW
15	Maia et al. (2019)	Y	Y	y	Y	Y	LOW	Y	Y	N	N	PN	HIGH	Y	Y	Y	Y	PN	HIGH	Y	Y	N	Y	Y	Y	HIGH	N	Y	Y	HIGH
16	Whelan et al. (2010)	Y	Y	N	Y	Y	HIGH	Y	Y	N	Y	Y	HIGH	Y	Y	Y	N	N	HIGH	Y	Y	N	Y	Y	N	HIGH	N	Y	Y	HIGH
17	Roquilly et al. (2014)	Y	Y	N	Y	Y	HIGH	N	Y	N	Y	PN	HIGH	Y	N	Y	Y	Y	HIGH	Y	Y	N	Y	N	N	HIGH	N	Y	Y	HIGH
18	Su et al. (2020)	Y	Y	Y	Y	Y	LOW	Y	PN	Y	Y	Y	HIGH	Y	Y	Y	Y	Y	LOW	Y	Y	N	Y	Y	Y	HIGH	N	Y	Y	HIGH
19	van Ruissen et al. (2019)	Y	Y	Y	Y	Y	LOW	Y	Y	PN	Y	PN	HIGH	PN	Y	Y	Y	PN	HIGH	Y	Y	Y	Y	Y	N	HIGH	N	Y	Y	HIGH
20	Weng et al. (2017)	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	PN	HIGH	Y	Y	N	Y	Y	N	HIGH	N	Y	Y	HIGH

Y, yes; PY, probably yes; PN, probably no; N, no; NI, no information

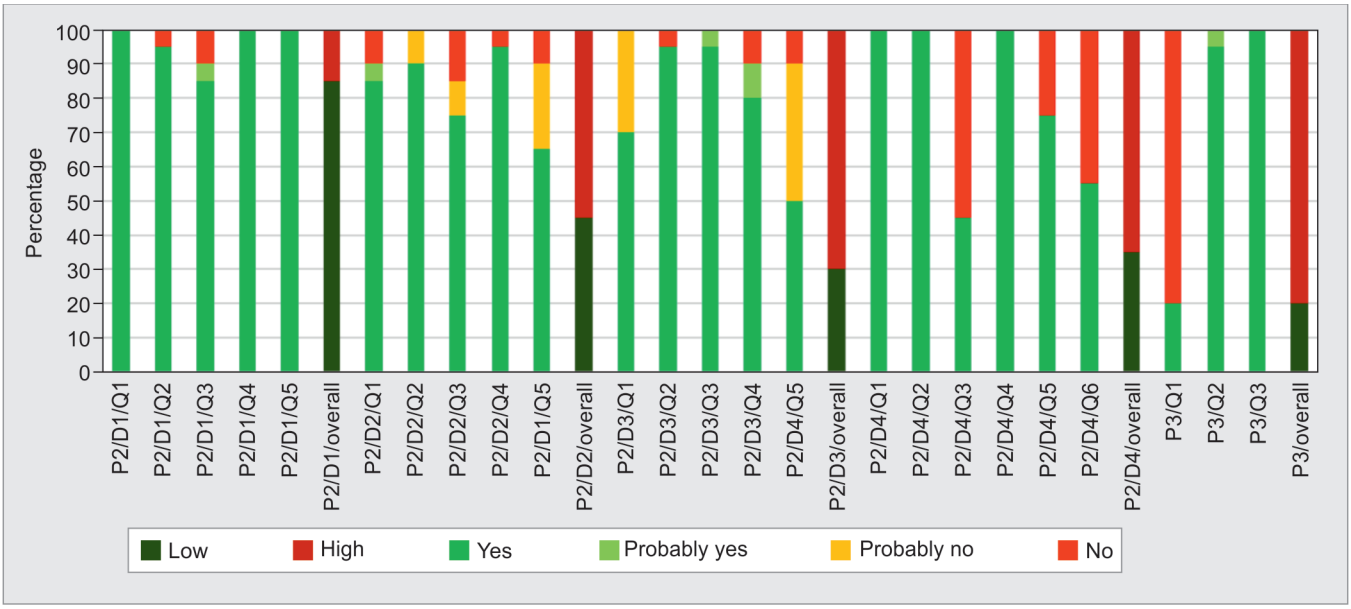

Fig. 1: Summary of the risk of bias assessment based on ROBIS tool. P, phase; D, domain; Q, question

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%.[35] VAP is the second most common nosocomial infection in the United States, after catheter-associated urinary tract infections.[36] 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.[37] A study comparing different interventions found probiotic a cost-effective intervention, in the prevention of VAP.[38] 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.[39] 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.[40] 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"*.[41] Also, the US National Institutes of Health (NIH) believes that the risk of harmful effects of living microbiota is greater for critically ill patients.[42] 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 stilled unclear.[43] 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.[44] Studies also reported that probiotics might lead to fungemia and bacteremia[45] and it should be used with caution in immune-compromised patients and older adults.[46]

A Cochrane review of pharmacological interventions for acute pancreatitis in 2017[47] 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.[48] These two studies

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.[49] The low quality of included studies is one of the most common limitations in the included SRs,[25,29,50] which should be considered in future studies. Also, publication bias is one of the other concerns.[28] 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.[51] 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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