

# The safety and efficacy of probiotic supplementation for critically ill adult patients: a systematic review and meta-analysis

Abdulaziz Sulaiman Alsuwaylihi  and Fiona McCullough

**Context:** The safety and efficacy of probiotics during severe illness has been a subject of ongoing interest. The impact of probiotics can worsen nutritional status, which could potentially result in a deterioration of the patient's overall life-threatening status. **Objective:** This systematic review and meta-analysis evaluated the safety and efficacy of probiotics in reducing intensive care unit (ICU)-acquired infections in adult critically ill patients. **Data Sources:** PubMed and Cochrane library databases for the period 2011–2020 were searched. **Data Extraction:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) methodology was used to search for randomized controlled trials that evaluated the use of probiotics among critically ill patients. **Data Analysis:** No significant difference was observed between probiotics and control groups in terms of the mortality rate (risk ratio 1.13, 95% confidence interval .82 to 1.55,  $P = .46$ ). Probiotics, however, provided a significant reduction in ICU-acquired infections (risk ratio .73, 95% confidence interval .58 to .93,  $P = .01$ ). **Conclusion:** The use of probiotics seems to play a role in decreasing the incidence of ICU-acquired infections. Also, a potential reduction in terms of the incidence of diarrhea has been reported, with no examples of adverse incidents, suggesting probiotics are safe.

## INTRODUCTION

Malnutrition, especially undernutrition in hospitalized patients, has attracted significant attention for decades.<sup>1</sup> Malnutrition has been defined as a lack of the nutrients required to sustain individual health, which can be caused by one or more factors such as inadequate intake, conditions leading to reduced absorption, high energy demands, and changes in the transporting

and utilization of nutrients.<sup>1</sup> The prevalence of malnutrition in hospitalized patients is between 30% and 50%, depending on the setting and the malnutrition criteria.<sup>1</sup> Many trials have demonstrated that nutritional management of malnourished patients lowers the risks of infection complication and wound inflammation, and the mortality rate.<sup>2</sup> Critically ill patients are often in a hypermetabolic state when they have life-threatening conditions such as trauma, burns, or

Affiliation: A. S. Alsuwaylihi is with the Department of Clinical Nutrition, King Saud Medical City, Riyadh, Saudi Arabia. F. McCullough is with the School of Biosciences Division of Food, Nutrition & Dietetics, University of Nottingham, Nottingham, UK.

Correspondence: Abdulaziz Alsuwaylihi, Department of Clinical Nutrition, King Saud Medical City, Al Imam Turki Ibn Abdullah Ibn Muhammad, Ulaishah, Riyadh 12746, Saudi Arabia 11196. E-mail: a.s.alsuwaylihi@gmail.com

*Key words:* critically ill, ICU, intensive care, critical care, prebiotics, probiotics, synbiotics, Lactobacillus, Bifido-bacterium.

© The Author(s) 2022. Published by Oxford University Press on behalf of the International Life Sciences Institute.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

systemic inflammatory response syndrome (SIRS).<sup>3</sup> The stomach/gastrointestinal tract has an immunoregulatory role that is influenced by the microbiota, the intestinal barrier, and the intestinal immune system.<sup>4</sup> With hyperinflammatory status, both the species composition and the numbers of the intestinal microorganisms are significantly changed, leaving the body exposed and unprotected against infections, which can lead to SIRS or multiple organ dysfunction syndrome (MODS).<sup>4</sup> Infections such as ventilator-associated pneumonia (VAP), sepsis, and urinary tract infections remain among the major causes of worsening of the patient's status or even death in critically ill patients.<sup>5</sup> Critically ill patients have an altered gut microbiome. The microbiome present in them consists more of pathogenic bacteria that cause various problems than of beneficial bacteria. In one study, the gut microbiomes of patients with severe SIRS were evaluated. The study found that the mean count of beneficial bacteria was lower and the mean *Pseudomonas* counts was higher. This was the first study to have shown an altered gut microbiome in critically ill patients.<sup>6</sup> Further study in SIRS patients has revealed that an altered gut microbiome results in enhanced gastrointestinal dysmotility, and that this leads to more complications and higher mortality in patients with SIRS.<sup>7</sup> In critically ill patients, beneficial commensals belonging to *Firmicutes* and *Bacteroidetes* are replaced by pathogens belonging to the Proteobacteria phylum. The change in the microbiome is due to the treatment of these patients with a wide range of antibiotics, which results in the loss of beneficial bacteria from the gut. Providing proper enteral nutrition would thus help in promoting the health of the patients. Several such therapies are taken into consideration and include probiotics, prebiotics, synbiotics, and fecal microbiota transplantation.<sup>8</sup> Diarrhea is identified by the frequency of three or more loose or liquid stools per day. It is a major clinical problem that can lead to undesirable outcomes, such as poor wound healing, shifting of the electrolyte balance, fluid losses, hemodynamic instability, and deficiency of nutrients.<sup>9</sup> Critically ill patients have diarrhea that is not infectious and has been observed to be related to the length of stay in hospital. Antibiotic-associated diarrhea is very common in critically ill patients, and there is a reported incidence of 5%–30%.<sup>10</sup> In patients who are receiving enteral feeding, it has been reported that the prevalence of diarrhea is 15% to 40%, or even higher.<sup>11</sup> A cohort study of 3737 patients showed that there was a higher prevalence of diarrhea in patients who stayed longer in hospital.<sup>12</sup> However, a study seeking to identify the critical factors related to the higher prevalence

has shown that microbes are not the major source, indicating the non-infectious nature of the diarrhea.<sup>12</sup>

The gastrointestinal tract of mammals hosts a large number of intestinal microorganisms that are important for maintaining good health. Many of these bacteria have been isolated and used for the treatment of a variety of gastrointestinal symptoms. These bacteria are termed “probiotics.” Administered probiotics function by inhibiting the action of pathogenic bacteria, helping immunomodulation, improving the barrier function of the gut, and helping the release of neurotransmitters. Thus, probiotics help in maintaining a healthy gut–brain axis. Probiotics belonging to the Bacteroidetes and Firmicutes phyla of bacteria have been used to treat a variety of intestinal symptoms, such as irritable bowel syndrome, diarrhea, inflammatory bowel disease, and antibiotic-induced diarrhea.<sup>13–15</sup> Randomized controlled trials (RCTs) using probiotics in critically ill patients have shown that patients receiving probiotic treatment had better immunity than placebo-treated patients. *Lactobacillus*, *Bifidobacterium*, and *Streptococcus salivarius* subsp. have all been used for treatment. Both *Lactobacillus* and *Bifidobacterium* are known to have beneficial effects on the gut.<sup>16</sup> VAP is a common occurrence in critically ill patients. A meta-analysis study on the use of probiotics and the outcome in terms of various parameters in critically ill patients showed that the use of probiotic treatment leads to a significant reduction in VAP incidence, length of intensive care unit (ICU) stay, in-hospital mortality, and duration of mechanical ventilation. In the systematic review, the use of a wide variety of probiotics was represented.<sup>17</sup> However, a contrary report has been published wherein the use of *Lactobacillus rhamnosus* GG for lowering VAP in critically ill patients was shown to be ineffective in reducing VAP.<sup>18</sup> Further research is needed to determine whether the use of *Lactobacillus rhamnosus* GG really helps in lowering the incidence of VAP.

The American Society of Parenteral and Enteral Nutrition (ASPEN) states that using probiotics is not recommended as routine practice, enterally or parenterally.<sup>19</sup> However, some studies have reported that probiotic use significantly reduces the infection incidence.<sup>20–22</sup> A few studies support the administration of probiotics in adult patients with diarrhea,<sup>23,24</sup> but no studies have recommended using probiotics as a diarrhea treatment in critically ill patients.<sup>9</sup> The presence of many strains and species of probiotics makes the studies on probiotics more challenging, and it is important to determine whether one or a combination of two strains will have a favorable outcome.<sup>9</sup> This review aimed to evaluate the safety and effectiveness of probiotics usage

to decrease ICU-acquired infection incidence in critically ill adult patients.

## METHODS

### Search strategy and article selection

Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA)<sup>25</sup> methodology was used to search for RCTs that evaluated the use of probiotics among critically ill patients. Two scientific databases, PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL), were searched independently by 2 investigators for relevant reports published between 2011 and 2020. Key words used included “critically ill” OR “ICU” OR “intensive care” OR “critical care” AND “prebiotics” OR “probiotics” OR “synbiotics” OR “*Lactobacillus*” OR “*Bifidobacterium*”.

### Inclusion criteria and exclusion criteria

Table 1 shows the PICOS (Participants, Intervention, Comparators, Outcomes, and Study Design) criteria. Studies were considered in this review if they evaluated the effect of probiotics on mortality, ICU-acquired infection, and diarrhea in adult critically ill patients (ventilated or nonventilated). Only RCTs were included in this review. Systematic reviews, case studies, conference abstracts, observational studies, interventions that included synbiotics or prebiotics, and papers that were not in English were all excluded from this review.

### Quality assessment and quality of the evidence

The quality assessment was performed using the modified Cochrane Collaboration tool to assess the risk of bias of an RCT on the basis of a judgment (high, low, or unclear) regarding individual elements from 5 domains: selection, reporting, performance, attrition, and other.<sup>26</sup>

The grading of the recommendations, assessment, development, and evaluation (GRADE) was used to assess the quality of the evidence.<sup>27</sup> Usually, RCTs start as being considered to have a high quality of evidence, which is then potentially downgraded to an assessment of having a moderate, low, or very low level of evidence, based on 5 domains (risk of bias, imprecision, heterogeneity, indirectness, and publication bias).

### Statistical analysis

In this review, the meta-analysis was conducted using Review Manager (RevMan v.5.4.1, Cochrane Collaboration, Oxford, UK). The mean difference

Table 1 PICOS criteria for inclusion of studies

Parameter	Criteria
Population	Adult critically ill patients who are admitted to ICU
Intervention	Single or multi-strains of probiotics
Comparison	Unexposed group (no probiotics)
Outcome	Mortality incidences, intensive care unit-acquired infections (such as pneumonia, urinary tract infection, and bloodstream infections) and incidence of diarrhea
Study design	Randomized controlled trials that are published in the English language

(MD), standard deviation (SD), and a random effect for the continuous variables were used to pool the data. Heterogeneity was assessed using the  $I^2$  test and was considered as “low” if  $I^2$  was  $\leq 25\%$ , “moderate” if  $I^2$  was  $>25$  but  $<75\%$ , or “high” if  $I^2$  was  $\geq 75\%$ .

## RESULTS

### Studies included

The trial flow diagram is presented in Figure 1. The initial search results revealed 2045 articles. Of these, 2006 articles were excluded due to being unrelated to the topic. An additional 29 were also excluded, for the following reasons: 2 trials were eliminated because they were not in the English language; 2 trials were eliminated due to the absence of desirable outcome; 2 trials were excluded because they only used synbiotics, and another trial was not performed on critically ill patients; finally, 22 trials were excluded because they were not performed on adult patients. A total of 9 RCTs were included in this study.

### Study characteristics

An aggregation of 9 RCTs<sup>4,9,28–34</sup> published between 2011 and 2020, with 860 critically ill patients from different ICUs, was evaluated. Six studies reported on the incidence of ICU mortality.<sup>4,29–32,34</sup> Seven studies reported on the incidence of ICU-acquired infections.<sup>4,29–34</sup> Five studies reported on the incidence of diarrhea.<sup>4,9,28,30–32</sup> Table 2<sup>4,9,28–34</sup> briefly summarizes the RCTs included in this review that evaluated the effectiveness of probiotics in critically ill patients.

### Quality assessment and quality of the evidence

Risk of bias (high, low, or unclear) was assessed on the basis of 5 domains: selection, reporting, performance, attrition, and other. Regarding the level of the evidence,

**Table 2 Summary of the included studies in this review, which evaluated the effectiveness of probiotics in critically ill patients, with reporting of the clinical outcomes**

Reference	Study design	Population (n)	Probiotic strain	Age as mean $\pm$ SD (years)	Outcomes	Comments
Wang et al (2020) <sup>4</sup>	A single-blind, RCT	T = 27 C = 33	<i>Clostridium butyricum</i>	81	ICU mortality: $P = .98$ ICU-acquired infections: $P = .91$ Incidence of diarrhea: $P = .12$	<ul style="list-style-type: none"> <li>patients were only from a respiratory unit</li> <li>small sample size</li> <li>elderly group of patients</li> </ul>
Ferrie and Daley (2010) <sup>9</sup>	A prospective, double-blind, RCT	T = 18 C = 18	<i>Lactobacillus rhamnosus</i> GG	58.95 $\pm$ 18.45	ICU mortality: not reported ICU-acquired infections: not reported Incidence of diarrhea: $P = .099$	<ul style="list-style-type: none"> <li>a significant difference in factors that influence diarrhea</li> <li>short treatment duration</li> <li>small sample size</li> </ul>
de Castro Soares et al (2017) <sup>28</sup>	A prospective, double-blind, pilot RCT	T = 29 Fiber = 29	<i>Bacillus cereus</i>	67.9 $\pm$ 19.4	ICU mortality: not reported ICU-acquired infections: not reported Incidence of diarrhea: $P = .011$	<ul style="list-style-type: none"> <li>used different types of nutrition formulation</li> <li>patients were on antibiotics</li> <li>absence of pure control group</li> <li>pilot study</li> <li>elderly group of patients</li> </ul>
Habib, Kassem, and Ahmed (2020) <sup>29</sup>	A double-blind, RCT	T = 32 C = 33	<i>Lactobacillus delbrueckii</i> and <i>Lactobacillus fermentum</i>	39.48 $\pm$ 7.69	ICU mortality: $P = 1.00$ ICU-acquired infections: $P = .75$ Incidence of diarrhea: not reported	<ul style="list-style-type: none"> <li>80% of the participants were males</li> <li>small sample size</li> <li>patients were only from the trauma unit</li> <li>a combination of 2 probiotics were used</li> </ul>
Kwon et al (2015)	A prospective, pilot RCT	T = 50 C = 53	<i>Lactobacillus rhamnosus</i> GG	62	ICU mortality: $P = .88$ ICU-acquired infections: $P > .05$ Incidence of diarrhea: not reported	<ul style="list-style-type: none"> <li>a significant difference in factors that influence infections</li> <li>small sample size</li> <li>short follow-up duration</li> <li>pilot study</li> </ul>
Mahmoodpoor (2018) <sup>31</sup>	A prospective, double-blind, RCT	T = 48 C = 52	Multistrains	58.3 $\pm$ 13.7	ICU mortality: $P = .58$ ICU-acquired infections: $P = .04^*$ Incidence of diarrhea: $P = .08$	<ul style="list-style-type: none"> <li>used different strains and species of probiotics</li> <li>most patients were from a surgical unit</li> <li>small sample size</li> </ul>
Rongrunruang et al. (2015) <sup>32</sup>	A prospective, open-label, RCT	T = 75 C = 75	<i>Lactobacillus casei</i>	71.02 $\pm$ 15.8	ICU mortality: $P = .85$ ICU-acquired infections: $P = .46$ Incidence of diarrhea: $P = .32$	<ul style="list-style-type: none"> <li>the trial was an open-label study</li> <li>medications use was not clearly reported</li> <li>small sample size</li> <li>elderly group of patients</li> </ul>
Tan et al (2011) <sup>33</sup>	A prospective, pilot RCT	T = 26 C = 26	Multistrains	40.6 $\pm$ 12.9	ICU mortality: not reported. ICU-acquired infections: $P = .095$	<ul style="list-style-type: none"> <li>missing tests that may affect the results</li> <li>small sample size</li> </ul>

(continued)

Table 2 Continued

Reference	Study design	Population (n)	Probiotic strain	Age as mean $\pm$ SD (years)	Outcomes	Comments
Zeng et al (2016) <sup>34</sup>	An open-label, RCT, multicenter	T = 118 C = 117	<i>Bacillus subtilis</i> and <i>Enterococcus faecalis</i>	52.4 $\pm$ 18.05	Incidence of diarrhea: not reported ICU mortality: $P = .2$ ICU-acquired infections: $P = .03^*$ Incidence of diarrhea: not reported	<ul style="list-style-type: none"> <li>• pilot study</li> <li>• absence of placebo-control</li> <li>• only patients with TBI</li> <li>• the trial was an open-label study</li> <li>• missing tests that may affect the results</li> <li>• small sample size</li> <li>• a combination of 2 probiotics were used</li> </ul>

\* $P < .05$  indicated a statistically significant difference. Abbreviations: C, control group; ICU, intensive care unit; n, number; RCT, randomized control trial; SD, standard deviation. TBI, traumatic brain injury; T, treatment group.

5 studies were rated as having a “high risk of bias.”<sup>9,30,32–34</sup> In addition, 4 studies were rated as having an ‘unclear risk of bias’.<sup>4,21,22,24</sup> The RCTs were graded based on 5 domains: risk of bias, imprecision, heterogeneity, indirectness, and publication bias. Figure 2 shows the risk-of-bias graph, and Figure 3 shows the risk-of-bias summary of all the included studies.

Table 3 shows the summary of the findings regarding the quality of the evidence, the risk of ICU mortality, and the risk of incidence of ICU-acquired infections. The quality of the evidence was downgraded to an assessment of a moderate level of certainty due to most of the included studies being rated as having a “high risk of bias.”

### ICU mortality

Data on ICU mortality were reported in 6 trials.<sup>4,29–32,34</sup> No effect of probiotics on ICU mortality was detected when compared with ICU mortality for the standard fiber groups,  $P > .05$ . Rongrungruang et al<sup>32</sup> conducted a trial on 150 critically ill patients, which did not report a significant difference between ICU mortality in the probiotic and control groups, (24% and 22.7%, respectively,  $P = .85$ ). Similarly, Kwon et al<sup>30</sup> conducted a trial on 103 critically patients, and no significant difference was observed between the probiotics and control groups in terms of death incidence (22% and 21%, respectively,  $P = .80$ ). In addition, in a multicentre RCT performed by Zeng et al<sup>34</sup> on 235 patients, there was no significant difference between the probiotic and control groups in either ICU (12.7% and 7.7%,  $P = .2$ ) or hospital (10.7% and 14.8%,  $P = .369$ ) mortality rates. Moreover,

Mahmoodpoor et al<sup>31</sup> carried out a double-blind RCT performed on 100 patients who were admitted to the ICU and undergoing mechanical ventilation. No significant difference in ICU mortality was observed between the probiotic and control groups (10.4% and 11.1%, respectively,  $P = .58$ ). A more recent RCT published in July 2020 was conducted by Habib, Kassem, and Ahmed<sup>29</sup> on 65 critically ill patients. No significant difference in ICU mortality was noticed between the 2 groups, (34.38% in the probiotics group and 36.36% in the control group,  $P = 1.0$ ). The most recent RCT, published August 2020, was performed by Wang et al<sup>4</sup> on 61 critically ill patients. They, too, did not report a significant difference between the probiotics and control groups (21% in each group,  $P = .98$ ). There was also no significant difference between probiotic and control groups in terms of the mortality rate at 3 months, (33.3% and 34.7%, respectively,  $P = .86$ ). When probiotics were given to adult critically ill patients compared with a control group, the meta-analysis found no significant reduction in mortality (risk ratio 1.13, 95% CI .82 to 1.55,  $P = .46$ , Figure 4).<sup>4,29–32,34</sup>

### ICU-acquired infections

Six trials<sup>4,29,30,32–34</sup> reported data regarding the infection incidence. In the Tan et al<sup>33</sup> study, conducted on 52 traumatic brain injury patients, the aim was to assess the effect of enteral administration of probiotics on the clinical outcomes for the patients and on regulating the serum of their immune cell receptors. The authors suggested that probiotics reduced the infection risk, but no statistically significant difference was observed in terms of infections between the probiotics and control groups

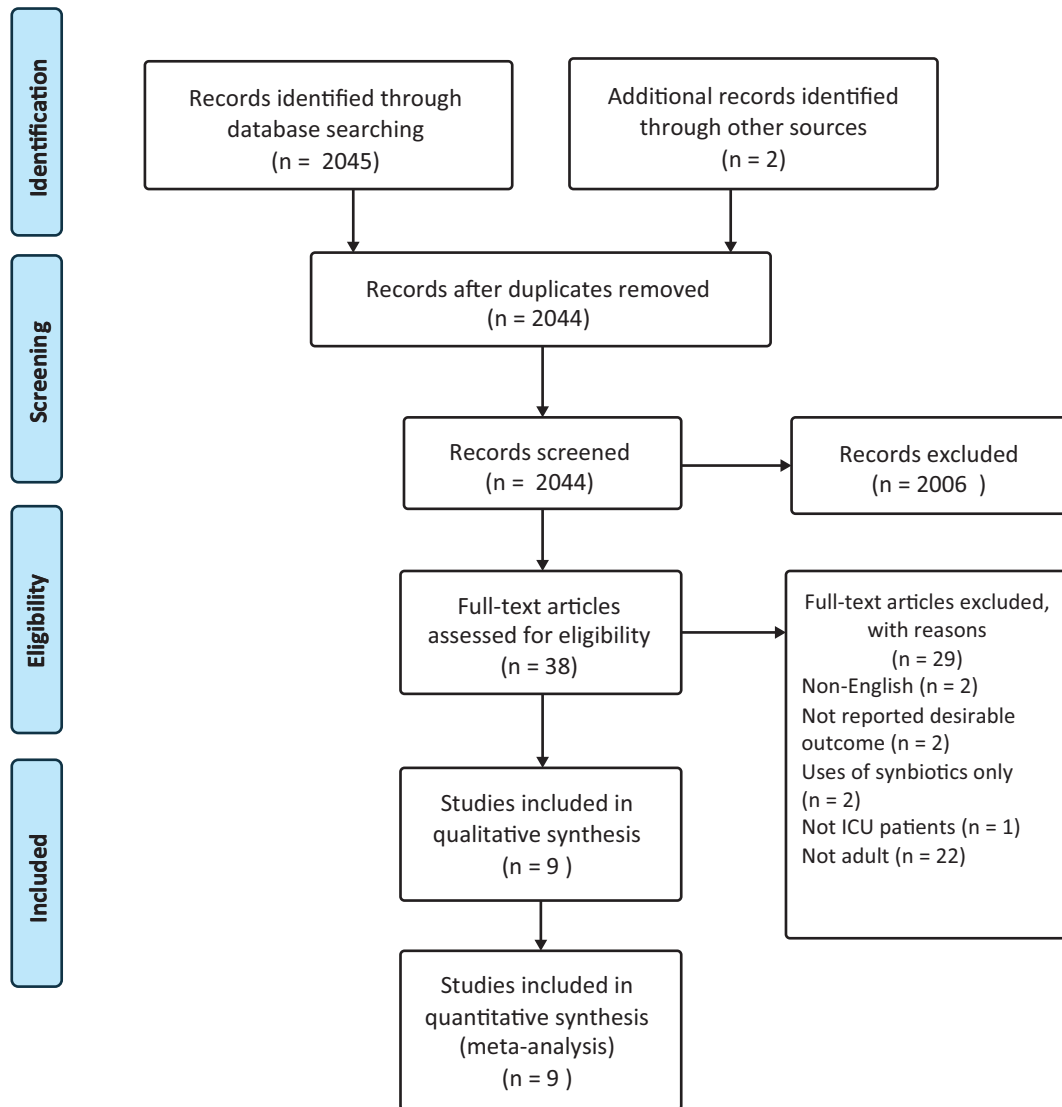


Figure 1 PRISMA flow diagram.

Abbreviations: ICU, intensive care unit; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses (Moher et al 2009<sup>25</sup>).

(34.6% and 57.7%, respectively,  $P = .095$ ). Moreover, in the Kwon et al<sup>30</sup> trial, the authors reported there was no significant difference between the probiotics and control groups  $P > .05$ . Rongrungruang et al<sup>32</sup> and Wang et al<sup>4</sup> concluded in their trials that there was no significant difference in terms of ICU infection,  $P = .46$  and  $P = .92$ , respectively, between the probiotics and control groups. In contrast, Zeng et al<sup>34</sup> and Mahmoodpoor et al<sup>31</sup> showed a significant reduction in terms of ICU-acquired infections, particularly regarding VAP infection,  $P = .031$  and  $P = .04$ , respectively. On the other hand, Habib, Kassem, and Ahmed<sup>29</sup> suggested that no significant difference was seen between the probiotics and control groups (15.6% and 21.21%, respectively,  $P = .75$ ) regarding VAP infection.

When probiotics were administered to one group and not to a control group, the meta-analysis found no significant difference in the incidence of ICU-acquired infections among adult critically ill patients (risk ratio .73, 95% CI .58 to .93,  $P = .01$ , Figure 5).<sup>4,29,30,32-34</sup>

### Incidence of diarrhea

Five trials reported data about the incidence of diarrhea.<sup>4,9,28</sup> An early RCT performed by Ferrie and Daley<sup>9</sup> was conducted on 36 critically ill patients. The result indicated that *Lactobacillus rhamnosus* GG increased the prevalence of daily loose stools, but this finding was not statistically significant,  $P = .099$ . No significant difference was observed in either per-protocol

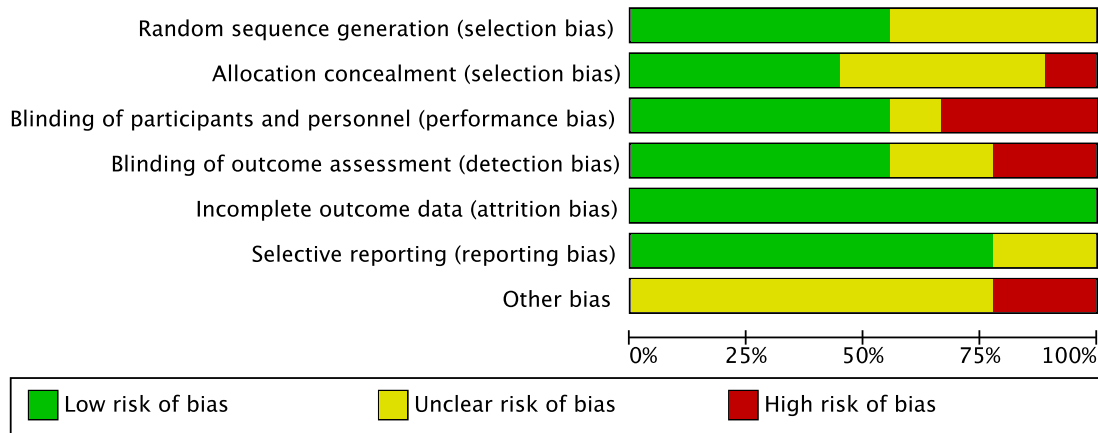


Figure 2 Risk-of-bias graph.

Review of authors' judgments about each risk-of-bias item presented as percentages across all included studies.

or intention-to-treat analyses in terms of the severity of diarrhea. In contrast, Rongrungruang et al<sup>32</sup> concluded that there was no significant difference in the diarrhea incidence between the probiotic and control groups (25.3% and 18.7%, respectively,  $P = .32$ ). A pilot study performed by de Castro Soares et al<sup>28</sup> conducted on 58 critically ill patients concluded that critically ill patients treated with *Bacillus cereus* A 05 probiotic had a significantly lower number of days with diarrhea than those treated with fiber,  $P = .011$ . The Mahmoodpoor et al trial<sup>31</sup> concluded that probiotics' use tends to reduce the incidence of diarrhea; however, no statistically significant difference was observed between the two groups (probiotics, 14.6%, control group, 27.8%,  $P = .08$ ). Furthermore, in a recent trial carried out by Wang et al,<sup>4</sup> no significant difference was noticed between the probiotic and control groups (43% and 24%, respectively,  $P = .12$ ).

## DISCUSSION

This review aimed at assessing the safety and efficacy of probiotics in reducing the occurrence of ICU-acquired infections in critically ill adult patients. Nutrition support has been developed over recent years, and it is now considered a crucial part of the treatment plan for critically ill patients.<sup>35</sup> Patients diagnosed with a systemic inflammatory disease, those with a long duration of hospitalization, and those with dysfunctions of multiple organs have a higher risk of morbidity and mortality rates due to various types of infection.<sup>35</sup> Before any nutritional intervention, patient safety must be ensured, especially in life-threatening situations. A previous systematic review and meta-analysis of 13 RCTs published by Barraud, Bollaert, and Gibot,<sup>36</sup> conducted on 1400 critically ill patients, reviewed a different strains of probiotics. In that study, it was concluded that probiotics

did not have any beneficial effect on the ICU mortality rate,  $P = .29$ . In addition, in another systematic review and meta-analysis of 8 RCTs performed by Bo et al<sup>37</sup> on 1083 critically ill patients, no significant difference was observed in terms of the mortality rate,  $P = .4$ . Manzanares et al<sup>38</sup> conducted a study on 2972 ICU patients to evaluate the effect of probiotics and synbiotics on critically ill patients and concluded that no significant difference was observed between the probiotics and control groups,  $P = .44$ , in terms of mortality incidence, which is consistent with the findings of the present review.

VAP is linked to a longer stay in the ICU and to mechanical ventilation.<sup>39</sup> In critically ill patients who are at a higher risk of infections, improved management and reduced risk of undesirable outcomes have been associated with the establishment and development of new approaches and interventions to evaluate the patient's status, resulting in better quality of care.<sup>5</sup> This review has found data supporting a significant reduction in ICU-acquired infections when probiotics are used: Manzanares et al<sup>38</sup> reported that the overall ICU infection and VAP incidence were significantly lower in the probiotics group,  $P = .009$ ,  $P = .002$ , respectively. In contrast, Barraud, Bollaert, and Gibot<sup>36</sup> reported that the use of probiotics did not show a beneficial effect in terms of ICU-acquired infections,  $P = .10$ . However, in a subgroup analysis of 10 trials, it was reported that there was a significant reduction in ICU-acquired pneumonia,  $P = .0005$ . In accordance with the main findings of Barraud, Bollaert, and Gibot<sup>36</sup>, Watkinson et al<sup>40</sup> has reported that uses of both probiotics and synbiotics were not associated with any significant difference between control and experiment groups regarding the rate of nosocomial infections, especially pneumonia.

Diarrhea is one of the most common complications among critically ill patients. Many factors can induce

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1. Wang et al 2020 (4)	?	?	+	+	+	+	?
2. Ferrie and Daley 2011 (9)	+	-	+	+	+	+	-
3. de Castro Soares et al 2017 (28)	?	+	?	+	+	?	?
4. Habib, Kassem, and Ahmed 2020 (29)	+	?	+	?	+	+	?
5. Kwon et al 2015 (30)	+	+	-	-	+	+	?
6. Mahmoodpoor et al 2018 (31)	+	+	+	+	+	+	?
7. Rongrungruang et al 2015 (32)	?	?	-	?	+	?	?
8. Tan et al 2011 (33)	+	+	+	-	+	+	-
9. Zeng et al 2016 (34)	?	?	-	+	+	+	?

Figure 3 Risk-of-bias summary.

Review of authors' judgments about each risk-of-bias item for each included study.

diarrhea in critically ill patients, such as pharmaceutical (eg, antibiotics, laxatives, and enemas), bowel infections, or other non-infective causes (eg, a lack of pancreatic enzymes, and overfeeding).<sup>12</sup> Studies have shown that diarrhea in critically ill patients is related to

adverse outcomes, such as developing wound infections, lowering the actual nutritional intake, dehydration, shifting and disturbance of the electrolytes, all of which ultimately increase the risk of mortality.<sup>8</sup> In this review, most of the included studies did not reveal any



**Table 3 Summary of findings**

Probiotic efficacy compared with placebo efficacy in critically ill patients  
 Patient or population: Critically ill patients  
 Setting: ICU  
 Intervention: Probiotic efficacy in critically ill patients  
 Comparison: Placebo

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with probiotic efficacy in critically ill patients
Mortality	683 (6 RCTs)	⊕⊕⊕○ Moderate <sup>a</sup>	RR 1.13 (0.82 to 1.55)	167 per 1000	<b>22 more per 1000</b> (30 fewer to 92 more)
ICU-acquired infection	563 (5 RCTs)	⊕⊕⊕○ Moderate <sup>a</sup>	RR 0.73 (0.58 to 0.93)	371 per 1000	<b>100 fewer per 1000</b> (156 fewer to 26 fewer)

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.

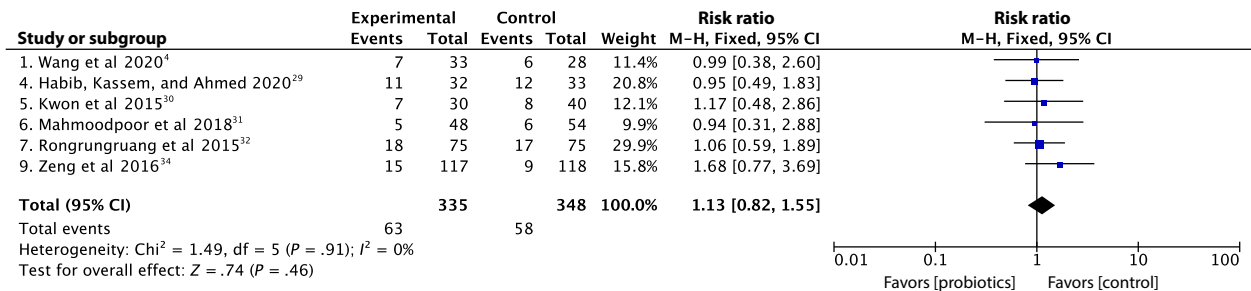
**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

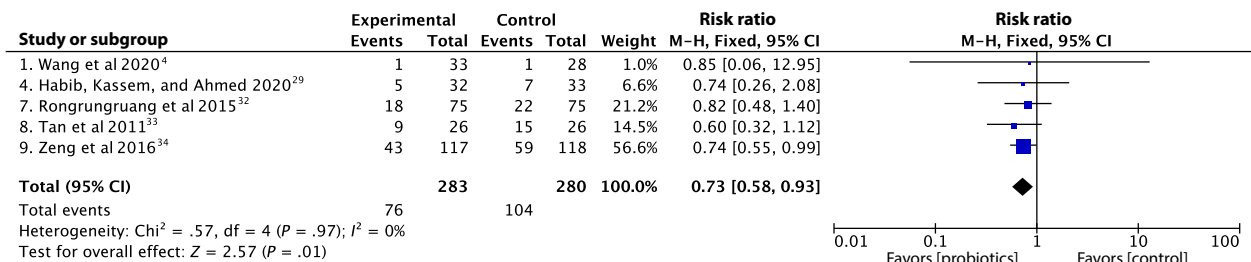
<sup>a</sup>Most of the included studies were rated as having a “high risk of bias.”

**\*The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). *Abbreviations:* CI, confidence interval; RR, risk ratio.



**Figure 4 Forest plot comparison: effect of probiotics on ICU mortality.**

*Abbreviations:* CI, confidence interval; ICU, intensive care unit; M-H, mantel-heanszel fixed-effect model.



**Figure 5 Forest plot comparison; effect of probiotics on ICU-acquired infections.**

*Abbreviations:* CI, confidence interval; ICU, intensive care unit; M-H, mantel-heanszel fixed-effect model.

significant effect of probiotics on preventing or reducing the incidence of diarrhea. Bo et al<sup>37</sup> reported that no significant difference was observed in terms of diarrhea incidence,  $P = .1$ . Consistent with the findings of the present review and Bo et al,<sup>37</sup> Manzanares et al<sup>38</sup> stated that no significant difference was observed between diarrhea incidence in probiotic and control groups,  $P = .74$ . On the other hand, *Saccharomyces boulardii* appears to be the most efficient fungus for preventing antibiotic-associated diarrhea, according to large single-strain meta-analyses: *S. boulardii* was found to have a pooled relative risk of 0.5, with 10 patients needing to be treated to prevent 1 case of antibiotic-associated diarrhea.<sup>41,42</sup> In addition, a recent systematic review and meta-analysis included studies (performed only in China) reporting that use of probiotics results in a significant reduction in terms of gastrointestinal complications among severe stroke patients  $P < .00001$ .<sup>43</sup>

This review has some strengths, including trials with double-blind designs, which minimizes the risk of bias and reduces the placebo effect. Also, most of the included trials used both intention-to-treat and per-protocol analysis to increase the reliability. However, this review has several limitations, such as a limited number of trials being reviewed with different levels of quality, which may impact the outcomes. Most of the studies were of a small sample size or a pilot design, which only provides an initial view of the effectiveness of the probiotics. A larger trial with a higher number of participants is required. This systematic review and meta-analysis investigated the effect of probiotics that were given via the enteral route, so these findings cannot be generalized to other feeding routes. Each trial used different probiotics strains and species, so it is challenging to determine the effect of a particular strain. Also, the higher age groups presented in some of the trials are usually linked with higher mortality rates than other age groups, and this could affect the mortality rate and the infection incidence, so the results cannot be generalized across all age groups. Two of the included studies<sup>32,34</sup> were of open-label design, impacting the clinician's management and/or patient outcomes. The medications and antibiotics that the patients were on were either not reported (as in Rongrungruang et al<sup>32</sup>) or administered in probiotic groups more than in control groups (as in Kwon et al<sup>23</sup>), which may affect the results for both ICU-acquired infections and incidence of diarrhea. A few trials were performed in specific ICU settings, such as respiratory and trauma units, so the results cannot be generalized across all ICU settings. Additionally, the trial tests that Zeng et al<sup>34</sup> used to confirm the VAP cases were less reliable than quantitative and microscopic examinations, which provide more accurate results. A few studies also looked at the

short period of the therapy and the follow-up for probiotic therapy, which was deemed insufficient to determine the actual effect of the probiotic on mortality or the infection rate. Moreover, in the trial of de Castro Soares et al,<sup>28</sup> the different formulas used (standard vs semi-elemental) was a factor. The semi-elemental formulas have a higher osmolality, which may induce an osmotic diarrhea,<sup>44,45</sup> in the de Castro Soares et al,<sup>28</sup> the participants were have one or more disease (cancer, lung diseases, heart disease, and other diseases) that affect the outcome due to the disease it self or due the medications that are used as a plan of the participants treatment plan. Finally, the absence of a pure control group tends to reduce the actual effect of the intervention.

## CONCLUSION

In conclusion, probiotics are considered a safe nutritional intervention among critically ill patients. The use of probiotics demonstrated an improved outcome in reducing the overall ICU infection rate, especially VAP. The uses of *Lactobacillus rhamnosus* GG and *Bacillus cereus* A 05 reduced the incidence of diarrhea among critically ill patients. However, the effectiveness of probiotics on the incidence of diarrhea remains inconclusive and limited. Probiotic effects are strain-specific, occur through a variety of pathways and mechanisms, and might differ depending on the illness state. As a result, the optimum probiotic dosage for critically ill patients remains unknown. Further trials with appropriate patients, using higher quality and specific probiotic strains would further assess the overall effectiveness of probiotics in critically ill patients.

## Acknowledgments

This article represents the original work of the authors and is not currently under consideration elsewhere, nor has it been previously published in the same or substantially similar form. No copyright for any other work was breached in the manuscript's creation.

*Author contributions.* A.A. is the first author who conceived and designed the study and the search strategy, screened the titles and abstracts, and full text, assessed the quality of the included studies, extracted and analysed the data, and wrote the manuscript. F.M. helped with drafting and revising the paper. All authors reviewed and provided comment on the manuscript. All authors read and approved the final manuscript.

*Funding.* There was no direct funding for the review.

**Declaration of interest:** The authors have no relevant interests to declare.

## REFERENCES

- Mueller C, Lord LM, Marian M, et al.; Nutrition ASPFAE. The ASPEN Adult Nutrition Support Core Curriculum. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017.
- BAPEN. BAPEN Publishes Results of Biggest Malnutrition Survey Ever Undertaken (Scotland). [www.bapen.org.uk](http://www.bapen.org.uk). Published February 7, 2018. Available at: <https://www.bapen.org.uk/media-centre/press-releases/377-bapen-publishes-results-of-biggest-malnutrition-survey-ever-undertaken-scotland>. Accessed December 14, 2020.
- Osooli F, Abbas S, Farsaei S, et al. Identifying critically ill patients at risk of malnutrition and underfeeding: a prospective study at an academic hospital. *Adv Pharm Bull*. 2019;9:314–320.
- Wang J, Ke H, Liu KX, et al. Effects of exogenous probiotics on the gut microbiota and clinical outcomes in critically ill patients: a randomized controlled trial. *Ann Palliat Med*. 2021;10:1180–1190.
- Hranjec T, Sawyer RG. Management of infections in critically ill patients. *Surg Infect (Larchmt)*. 2014;15:474–478.
- Shimizu K, Ogura H, Goto M, et al. Altered gut flora and environment in patients with severe SIRS. *J Trauma*. 2006;60:126–133.
- Shimizu K, Ogura H, Asahara T, et al. Gastrointestinal dysmotility is associated with altered gut flora and septic mortality in patients with severe systemic inflammatory response syndrome: a preliminary study. *Neurogastroenterol Motil*. 2011;23:330–335, e157.
- Moron R, Galvez J, Colmenero M, et al. The importance of the microbiome in critically ill patients: role of nutrition. *Nutrients*. 2019;11:3002.
- Ferrie S, Daley M. *Lactobacillus* GG as treatment for diarrhea during enteral feeding in critical illness. *JPEN J Parenter Enteral Nutr*. 2011;35:43–49.
- Szymański H, Pejcz J, Jawień M, et al. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains – a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther*. 2006;23:247–253.
- Murali M, Ly C, Tirlapur N, et al. Diarrhoea in critical care is rarely infective in origin, associated with increased length of stay and higher mortality. *J Intensive Care Soc*. 2020;21:72–78.
- Tirlapur N, Puthuchery ZA, Cooper JA, et al. Diarrhoea in the critically ill is common, associated with poor outcome, and rarely due to *Clostridium difficile*. *Sci Rep*. 2016;6:24691.
- Sánchez B, Delgado S, Blanco-Míguez A, et al. Probiotics, gut microbiota, and their influence on host health and disease. *Mol Nutr Food Res*. 2017;61:1600240.
- Ranjha MMAN, Shafique B, Batool M, et al. Nutritional and health potential of probiotics: a review. *Appl Sci*. 2021;11:11204.
- Sanjukta M, Swastik A. A brief overview on probiotics: the health friendly microbes. *Biomed Pharmacol J*. 2021;14:1869–1880.
- Alberda C, Gramlich L, Meddings J, et al. Effects of probiotic therapy in critically ill patients: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2007;85:816–823.
- Batra P, Soni KD, Mathur P, et al. Efficacy of probiotics in the prevention of VAP in critically ill ICU patients: an updated systematic review and meta-analysis of randomized control trials. *J Intensive Care*. 2020;8:81.
- Johnstone J, Meade M, Lauzier F, et al.; Prevention of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) Investigators and the Canadian Critical Care Trials Group. Effect of probiotics on incident ventilator-associated pneumonia in critically ill patients: a randomized clinical trial. *JAMA*. 2021;326:1024–1033.
- McClave SA, Taylor BE, Martindale RG, et al.; the Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) [published correction appears in *JPEN J Parenter Enteral Nutr*. 2016 Nov;40(8):1200]. *JPEN J Parenter Enteral Nutr*. 2016;40:159–211.
- Knight DJW, Gardiner D, Banks A, et al. Effect of synbiotic therapy on the incidence of ventilator associated pneumonia in critically ill patients: a randomized, double-blind, placebo-controlled trial. *Intensive Care Med*. 2009;35:854–861.
- van Santvoort HC, Besselink MG, Timmerman HM, et al. Probiotics in surgery. *Surgery*. 2008;143:1–7.
- Rayes N, Seehofer D, Theruvath T, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation – a randomized, double-blind trial. *Am J Transplant*. 2005;5:125–130.
- Wunderlich PF, Braun L, Fumagalli I, et al. Double-blind report on the efficacy of lactic acid-producing *Enterococcus* SF68 in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoea. *J Int Med Res*. 1989;17:333–338.
- Camarri E, Belvisi A, Guidoni G, et al. A double-blind comparison of two different treatments for acute enteritis in adults. *Chemotherapy*. 1981;27:466–470.
- Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred Reporting Items for Systematic reviews and Meta-Analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
- Higgins JP, Altman DG, Gøtzsche PC, et al.; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- GRADEpro. GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). 2020. Available at: <https://www.gradepr.org>. Accessed June 18, 2021.
- de Castro Soares GG, Marinho CH, Pitol R, et al. Sporulated *Bacillus* as alternative treatment for diarrhea of hospitalized adult patients under enteral nutrition: a pilot randomized controlled study. *Clin Nutr ESPEN*. 2017;22:13–18.
- Habib T, Kassem A, Ahmed I. Early probiotics in preventing ventilator-associated pneumonia after multiple trauma. *Asian J Pharm Clin Res*. 2020;13:83–85.
- Kwon JH, Bommarito KM, Reske KA, et al.; Centers for Disease Control and Prevention (CDC) Prevention Epicenters. Randomized controlled trial to determine the impact of probiotic administration on colonization with multidrug-resistant organisms in critically ill patients. *Infect Control Hosp Epidemiol*. 2015;36:1451–1454.
- Mahmoodpoor A, Hamishehkar H, Asghari R, et al. Effect of a probiotic preparation on ventilator-associated pneumonia in critically ill patients admitted to the intensive care unit: a prospective double-blind randomized controlled trial. *Nutr Clin Pract*. 2019;34:156–162. doi:10.1002/ncp.10191
- Rongrungruang Y, Krajangwittaya D, Pholtawornkulchai K, et al. Randomized controlled study of probiotics containing *Lactobacillus casei* (Shirota strain) for prevention of ventilator-associated pneumonia. *J Med Assoc Thai*. 2015;98:253–259.
- Tan M, Zhu J-C, Du J, et al. Effects of probiotics on serum levels of Th1/Th2 cytokine and clinical outcomes in severe traumatic brain-injured patients: a prospective randomized pilot study. *Crit Care*. 2011;15:R290.
- Zeng J, Wang C-T, Zhang F-S, et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. *Intensive Care Med*. 2016;42:1018–1028.
- Park YE, Park SJ, Park Y, et al. Impact and outcomes of nutritional support team intervention in patients with gastrointestinal disease in the intensive care unit. *Medicine (Baltimore)*. 2017;96:e8776.
- Barraud D, Bollaert P-E, Gibot S. Impact of the administration of probiotics on mortality in critically ill adult patients: a meta-analysis of randomized controlled trials. *Chest*. 2013;143:646–655.
- Bo L, Li J, Tao T, et al. Probiotics for preventing ventilator-associated pneumonia. *Cochrane Database Syst Rev*. 2014;10:CD009066.
- Manzanares W, Lemieux M, Langlois PL, et al. Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis [published correction appears in *Crit Care*. 2017 Feb 27;21(1):42]. *Crit Care*. 2016;19:262.
- Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. *Intensive Care Med*. 2020;46:888–906.
- Watkinson PJ, Barber VS, Dark P, et al. The use of pre- pro- and synbiotics in adult intensive care unit patients: systematic review. *Clin Nutr*. 2007;26:182–192.
- Szajewska H, Mrukowicz J. Meta-analysis: non-pathogenic yeast *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther*. 2005;22:365–372.
- McFarland LV. Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients. *World J Gastroenterol*. 2010;16:2202–2222.
- Liu X, Zhang Y, Chu J, et al. Effect of probiotics on the nutritional status of severe stroke patients with nasal feeding that receive enteral nutrition: a protocol for systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2021;100:e25657.
- Carteron L, Samain E, Winiszewski H, et al. Semi-elemental versus polymeric formula for enteral nutrition in brain-injured critically ill patients: a randomized trial. *Crit Care*. 2021;25:1–12.
- Pereira-da-Silva L, Dias MP-G, Virella D, et al. Osmolality of elemental and semi-elemental formulas supplemented with nonprotein energy supplements. *J Hum Nutr Diet*. 2008;21:584–590.