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SYSTEMATIC REVIEW

THE EFFECTS OF PROBIOTICS, PREBIOTICS AND SYNBIOTICS ON INFECTIONS AND CLINICAL OUTCOMES IN CRITICAL ILLNESS: A SYSTEMATIC REVIEW

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Abstract

Background: Critically ill patients treated in intensive care units (ICU) are characterized by a qualitative and quantitative change in the composition of their intestinal microflora, leading to a reduction in commensal flora and an overgrowth of potentially pathogenic bacteria, which increase susceptibility to nosocomial infections and compromise their outcome. Probiotics are live, non-pathogenic microorganisms that can provide health benefits to the host, such as restoring the balance of the microbiota and positive effects on immune function and gastrointestinal tract structure and function, when ingested in sufficient quantities. This systematic review aimed to evaluate the effects of probiotics/prebiotics and synbiotic mixtures on infections and clinical outcomes in critically ill patients.

Method and Material: Randomized clinical trials (RCTs) were reviewed in PubMed, EMBASE, CINAHL, CENTRAL and COHRANE from January 2004 to November 2024. Initially, 81 RCTs were selected, which evaluated the effects of probiotics or synbiotics versus placebo or prebiotics on clinical outcomes in adult ICU patients. Following the implementation of the PRISMA statement, 25 studies were finally included in this systematic review, and 5.106 patients were identified for analysis. The total number of new infections was the primary outcome. Secondary outcomes included mortality, ICU-acquired pneumonia, duration of mechanical ventilation (MV), length of stay (LOS) in the ICU, hospital and diarrhea.

Results: Probiotics were associated with a significant reduction in infections and ventilator-associated pneumonia (VAP), shorter duration of MV, ICU and hospital LOS and fewer episodes and shorter duration of diarrhea. No effect on ICU or hospital mortality was observed. Moreover, the greatest improvement in most outcomes was seen with probiotics alone compared to synbiotics mixtures, with a higher dose of probiotics (≥5 × 109 CFU/day) and with at least 14-15 days of supplementation.

Conclusion: Probiotics appear to reduce infectious complications, including ventilator-associated pneumonia, in critically ill patients and positively influence ICU and hospital LOS, days on MV and diarrhea. However, clinical heterogeneity and potential publication bias limit a clear clinical recommendation. Further research on probiotics in critically ill patients and more high-quality clinical trials are needed to demonstrate these benefits.

Keywords: Probiotics, prebiotics, synbiotic, critically ill patients, enteral nutrition.

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INTRODUCTION

Infections are the most common cause of death in adult patients admitted to Intensive Care Units (ICUs) in Europe, Asia, and America. Despite the heterogeneity of the clinical picture in critically ill patients, ICU patients have been found to exhibit a change in the composition of the gut microflora, i.e. the microbes that colonize the gut, with a reduction in "normal" bacteria and an increase in potentially pathogenic bacteria, a phenomenon known as 'dysbiosis', which increases the predisposition to developing hospital-acquired infections while compromising outcome.[1] Systemic infections can lead to an increased risk of complications and burdensome outcomes. Systemic infections include infections of the respiratory tract, urinary tract and bacteremia[2] and it has been shown that microbiome dysbiosis is not implicated as the cause of them, but as a critical mediator between external stimuli and systemic infections. Possible explanations for the dysbiosis of the microbiome in the severely ill are rapid changes in feeding parenteral and enteral nutrition, the stress they are under, the drugs that inhibit gastric acidity, antibiotics, mechanical ventilation etc.

As the intestinal mucosa been hypothesized to play a vital role in the progression of severe disease, sepsis and multiorgan dysfunction syndrome (MODS)[3], the maintenance of a healthy/physiological mucosa, possibly through probiotic administration, is of great interest in the literature. According to the World Health Organization (WHO), probiotics are defined as live non-pathogenic microorganisms, which when administered in sufficient quantity have shown beneficial effects in the prevention and treatment of various pathological conditions.[4]

To date, the mechanisms by which probiotics have been described through which they may exert beneficial effects include modification of the gut microbiome by enhancing antimicrobial peptide production, release of antimicrobial factors, suppression of immune cell proliferation, activation of mucus and IgA production, enhancement of the immune response and activation of various protective actions of the epithelial barrier. Considering that the gut plays an important role in the progression of severe disease, sepsis and MODS[3], strengthening the intestinal barrier and maintaining a normal intestinal microbiota, possibly through the administration of congenital bacteria (probiotics), has been shown by many studies to optimize the course of severely ill patients.[5,6,7] However, at the same time there are studies which have shown no improvement.[8]

As the administration of probiotics in the ICU remains widespread, while current guidelines are not completely clear, and at the same time there are a significant number of new clinical trials with the use of probiotics in critically ill patients, we considered it necessary to conduct a systematic review on the efficacy of probiotics use in the ICU. We aim to evaluate the efficacy of probiotic / prebiotic and /or synbiotic administration on both infections and overall outcomes in adult patients hospitalized in the intensive care unit.

METHODOLOGY

Protocol

This systematic review meets the relevant criteria of the Preferred Reporting Items for Systematic Reviews (PRISMA)[9] (Figure 1).

Eligibility criteria

The research question and the inclusion and exclusion criteria were defined as a priori and developed using a PICOS structure (Patient, Intervention/Exposure, Comparators, Outcome, Study Design). Only studies with clear information from the authors about their design were considered. The inclusion criteria were: (1) randomized, controlled, parallel, group-controlled trials; (2) adults aged ≥ 18 years, ICU patients; (3) probiotics or synbiotics or in combination compared with a control group (placebo or prebiotics) and (4) prespecified clinical outcomes in critically ill ICU patients such as primarily total infections and ventilator-associated pneumonia (VAP) and secondarily ICU and hospital mortality, ICU and hospital length of stay, ventilator length of stay, and incidence of diarrhea. We excluded studies that examined different outcomes, e.g., only nutrition-related, or only biochemical markers.

Information sources and search strategy

A literature search was conducted in the National Institutes of Health (NIH) via PubMed and EMBASE, CINAHL, CENTRAL and COHRAINE to find all randomized clinical trials (RCTs) published

from January 2004 to November 2024. The literature search combined the terms "enteral nutrition" as well as "probiotics" OR "prebiotics" OR "synbiotics" AND "critically ill patients". Only articles in English were considered.

Study selection and data extraction

Two reviewers (OK, VL) conducted the primary screening independently. Secondary screening in full text was also performed by two reviewers (OK, VL) to assess eligibility and exclude studies that did not meet the inclusion criteria.

Quality assessment

The methodological quality of the studies was assessed using the Jadad Score,[10] which consists of a point system from 1 to 5 according to the following criteria: (1) the study was described as randomized (this includes the use of words such as random, randomization), (2) the study was described as double-blind, (3) there was a description of subjects who dropped out or withdrew from the study. The first two questions can be scored 0 to 2 and the third 0 to 1. Regarding the comparison between groups, in the studies where p values were used, we considered statistically significant differences as those with $p < 0.05$ and the variables with $p < 0.10$ were considered as indicating a trend.

Clinical outcomes - subgroup analysis

As mentioned above, the main clinical outcomes studied were total infections, VAP, ICU/hospital mortality, length of ICU/hospital stay, duration of MV and incidence of diarrhea. Our secondary aim is to report the results of the studies on the above key outcomes to important intervention modifiers, such as (1) the administration of a probiotic, a prebiotic or a combination of both, i.e. a synbiotic, (2) the dose administered, with a high dose defined as the higher of 5 billion colony forming units (CFU) / day and a low dose defined as the lower of 5 billion CFU / day (73), and (3) the days of microbial administration in 7-day intervention, 14-15-day intervention and intervention longer than 15 days.

RESULTS

Identification and selection of clinical studies

A total of eighty-five relevant citations of randomized clinical trials were identified by searching computerized bibliographic databases and reviewing reference lists of related articles. Of these, we excluded fifty-three studies for the following reasons: 43 articles were systematic reviews, 7 were Meta- analyses, 1 was a letter to the editor and 2 were pilot studies. Of the 32 remaining studies, 7 additional studies were excluded because 2 involved a pediatric population, 2 clinical trials had only one intervention group and no second control group, 1 other study administered only a diet and no probiotics, and 2 studies examined different outcomes, i.e., had only nutritional and biochemical markers as outcomes (Figure 1).

Characteristics of the Clinical Trials

Finally, twenty-five randomized clinical trials [7,8,11–33] met the standards to be included in our systematic review. All trials were published after 2004 and included 5106 patients treated in the ICU (Tables 1 and 2). The average methodological quality of the studies was 4.12 with a maximum of 5 and a minimum of 2. Details of the qualitative analysis of the studies can be found in Table 1. All but 9 of the studies were conducted at a single research center. 16 studies were double-blind studies, 6 were single-blind studies and the remaining 3 were non-blind studies. The number of patients also varied, ranging from 17[13] to 2650[31] with a mean of 204 patients.

The probiotic interventions - treatments - used in the studies varied widely between studies. 18 studies administered probiotics alone, while 7 studies chose to administer synbiotics and 0 studies with prebiotics alone. 11 studies administered lactobacilli alone, 2 lactobacilli and enterococci, 3 lactobacilli and bifidobacteria, 7 lactobacilli, bifidobacteria and streptococci, 1 enterococcus alone, 1 clostridium butyricum alone. The probiotics were administered either orally or through gastric tube GT, orogastric tube OG or nasogastric tube NGT and the daily dose of probiotics administered ranged from $5*10^{7}$ [8] to $2*10^{11}$ CFU.[17] The control groups received enteral nutrition and/or parenteral nutrition with or without placebo (4 groups received enteral nutrition and prebiotics).[18,20,22,25]

Primary results

New infections overall

Treatment with probiotics led to a lower incidence of infections in the group receiving the probiotics than in the control group. When we summarize the results of the 25 studies, we find that 12 studies reported on the total number of infections that occurred during hospitalization in the ICU and 5 of them[12,14,15,17,24] showed a statistically significant lower incidence of infections in the intervention group. At the same time, 4 of the remaining 7 studies[8,20,21,22] showed a lower tendency to develop infections in the intervention group, 1 showed no difference[31] and only 2 showed a greater tendency.[11,30]

Ventilator-associated pneumonia

Treatment with probiotics resulted in a lower incidence of ventilator-associated pneumonia in the group receiving probiotics than in the control group. Of the total of 25 studies, 15 reported on VAP and 9 of them[7,15,17,18,24,25,26,28,32] showed a statistically significant lower incidence of VAP in the intervention group. At the same time, 4[16,21,27,33] of the remaining studies showed a lower tendency to develop VAP in the intervention group and only 2 studies[20,31] showed a greater tendency, but these differences were not statistically significant.

Mortality in the intensive care unit

Treatment with probiotics does not appear to affect ICU mortality, as none of the 19 out of 25 studies comparing the probiotic-treated group with the control group showed statistically significant results. The trends between the studies were also different: 12 studies[13,14,16,17,18,20,21,24,25,27,31,33] showed lower patient mortality in the intervention group, 3 studies showed the same values in both groups[8,29,30] and 4 studies[7,15,19,26] showed increased mortality in the intervention group.

In-hospital mortality

The results on in-hospital mortality were presented in 7 studies, none of which showed statistically significant differences between the group receiving probiotics and the group not receiving probiotics. However, we note that 5 studies[7,11,13,16,31] showed a lower mortality rate in the intervention group, 1 study[22] showed the same mortality rate and only 1 study[30] showed a higher mortality rate in both groups.

Length of stay with mechanical ventilation.

The administration of probiotics appeared to have a positive effect on MV, as out of the 14 studies[7,12-18,23,25,27,28,31,33] that reported on the duration of MV between patients in the intervention and control groups, 8 studies[7,12,13,15,17,23,25,33] showed that the group receiving probiotics spent fewer days on mechanical ventilation and 5 of them[12,14,17.23,25] with a statistically significant difference. 5 out of the rest studies showed the same duration of MV between patients in the intervention and control groups[16,18,28,31,33] only 1 of them[27] showed more days of MV, but these differences were not statistically significant.

Length of stay in the intensive care unit.

Treatment with probiotics appeared to reduce the days of ICU stay. The length of ICU stay was examined in 22 of 25 studies and the results of 9 of the studies[12,14,17,21,23,25,26,29,32] showed a statistically significant reduction in ICU days in the probiotic group. The results of the remaining studies that did not show statistical significance were different: 7 studies[7,13,14,16,19,20,24,28] showed a shorter ICU stay for the intervention group, 4 studies[8,11,22,27] showed a longer ICU stay and 2 studies[18,31] showed the same duration.

Length of hospital stay. The length of hospital stay in the intensive care unit was investigated in 11 clinical studies, whereby the results of 10 studies were not statistically significant and differed from each other. However, one study showed statistically significantly fewer days of hospitalization for the group in which probiotics were administered.[25]

Incidence of diarrhea

The administration of probiotics to ICU patients appears to have a positive effect on the incidence of diarrhea, as of the 8 clinical trials, 2[18,19] showed a lower incidence of diarrhea episodes or fewer days with diarrhea in the group receiving probiotics, and another trial[25] showed a trend towards similar results.

Secondary results

Intervention with probiotics or synbiotic

Among the 25 randomized clinical trials, there was considerable heterogeneity in terms of the type of intervention, with 18 trials exclusively administering probiotics and the remaining 7 trials administering synbiotics. As for the statistically significant results:

- In the occurrence of fewer infections in the intervention group, 4 had administered synbiotics[14,15,17,24] and one had administered probiotics.[12]
- In the occurrence of fewer cases of ventilator-associated pneumonia in the intervention group, 4 studies[15,17,24,28] had administered synbiotics, while the other 5[7,18,25,26,28,32] had administered probiotics.
- With the shorter duration of mechanical ventilation in the intervention group, 6 studies[7,12,13,23,25,33] had administered probiotics and only 2 studies[15,17] had administered synbiotics.
- With the shorter length of stay in the intensive care unit in the intervention group, 7 studies[12,21,23,25,26,29,32] had administered probiotics and only 2 studies[14,17] synbiotics.
- Probiotics were administered for the shortest length of hospital stay in the intervention group.[25]
- Fewer episodes of diarrhea occurred in the intervention group that was administered probiotics[18,19] while the study showing a tendency for fewer episodes of diarrhea had also administered probiotics.[25]

  Probiotics have a statistically significant effect on more of the primary endpoints assessed than synbiotics.

The dosage used.

Among the 25 randomized clinical trials, there was also great heterogeneity in the dosage of the administered bacteria. 18 studies[7,11,14-17,29-33,25,26,28,30-33] administered a high dose of microbiota ≥ 5 billion CFU colony forming units/day and the remaining 7[8,12,13,18,24,27,29] studies administered a dose ≤ 5 billion CFU/day.

Regarding the statistically significant results:

- In the occurrence of fewer infections in the intervention group, 2 had administered a small dose[12,24] and the other 3 a large dose.,14,15,17
- In the occurrence of fewer cases of ventilator-associated pneumonia in the intervention group, 2 studies[18,24] had administered a small dose, while the other 7 had administered a larger dose[7,15,17,25,26,28,32]
- On the shorter duration of stay on mechanical ventilation in the intervention group only 2 studies had administered a small dose[12,13], whereas the other 6 administered a large dose[7,15,17,23,25,33]
- On the shorter duration of stay in the ICU in the intervention group in 2 studies[12,29] had administered a small dose, while the other 7 had administered a large dose.[14,17,21,23,25,26,32]
- On the shorter length of hospital stay in the intervention group a large dose was administered.[25]
- In the occurrence of fewer episodes of diarrhea in the intervention group, one study administered a large dose[19] and the other a small dose[18], while the study showing a tendency for fewer episodes of diarrhea had administered a large dose of probiotics.[25]

  Larger doses have a statistically significant effect on more of the primary endpoints tested than lower doses.

The length of administration of probiotic

Among the 25 randomized clinical trials, there was also great heterogeneity in terms of the days of administration of the microbiota. 2 studies[22,23] administered probiotics for 7 days, 6 studies for 10-15 days[7,11,12,14,17,25] and the remaining 17 studies for >15 days[8,13,15,16,18-21,24,26-34]

As for the statistically significant results:

- Regarding the occurrence of fewer infections in the intervention group, 3 studies[12,14,17] administered the microbiota for 14 or 15 days, 2 studies[15,24] administered the probiotics for longer than 15 days.
- With fewer cases of ventilator-associated pneumonia in the intervention group, 3 studies[7,17,25] administered probiotics for 10-15 days and 6 studies[15,18,24,26,28,32] and 6 studies[15,18,24,26,28,32] for >15 days.

- With the shorter duration of mechanical ventilation in the intervention group, 4 studies[12,14,17,25] administered probiotics for 10-15 days and 1 study[23] for 7 days.
- On the shorter duration of ICU stay in the intervention group, 4 studies[12,14,17,25] had administered probiotics for 10-15 days, other 4 studies[21,16,29,32] had administered probiotics for >15 days, while only 1 study[23] had administered probiotics for 7 days.
- On the shorter duration of hospitalization in the intervention group, probiotics had been administered for 14 days.[25]
- Regarding the occurrence of fewer episodes of diarrhea in the intervention group, both studies had administered probiotics for >15 days[18,19], while the study showing a trend towards fewer episodes of diarrhea[25] had administered probiotics for 14 days.

  As you can see from the above, most of the statistically significant results were related to the number of probiotics given for 14 days or longer.

Safety issues

Safety issues regarding the administration of probiotics were investigated in 7 RCTs. Treatment with probiotics/synbiotics proved to be safe in the group of critically ill patients in the intensive care unit in 6 out of 7 RCTs.[7,15,18,20,21,25] Neither adverse effects associated with probiotics nor infections or bacteremia due to the strains used in these studies were reported. Only in 1 large RCT[31] 16 patients (15 of them were receiving probiotics (1.1%) compared with 1 patient (1.1%) receiving placebo) experienced either an adverse event or a serious adverse event -2 patients who had a serious adverse event died.

DISCUSSION

In this systematic review of 5106 ICU patients, the association between treatment with microbials, i.e., probiotics and/or synbiotics and the outcome of these patients was investigated. The administration of probiotics/synbiotics was associated with a statistically significant reduction in overall ICU infections, including ventilator-associated pneumonia, which is the most common infection in critically ill patients. Our findings on reducing overall infections and VAP are consistent with previous large systematic reviews.[35-41] However, there have been other large systematic reviews in the past, such as that by Barraud et al[42], which did not show a positive contribution of probiotic administration to overall infections but also indicated a positive effect of probiotic treatment on VAP. The administration of probiotics may contribute to the reduction of VAP and other nosocomial infections by restoring non-pathogenic bacteria in the gut microflora that compete with pathogenic nosocomial microbes by inhibiting their proliferation, modifying local and systemic immune responses, and improving intestinal barrier function[43]. Despite reducing nosocomial infections and VAP, probiotics do not appear to influence ICU or hospital mortality, as none of the trials found such an effect. This may seem contradictory, but after all, mortality due to VAP is lower than previously thought.[44] However, Lou et al.[39] reported that probiotic and synbiotic supplements are beneficial for ICU mortality, but they also wrote that sensitive analysis showed that no single study qualitatively altered the pooled mortality of ICU, providing evidence for the stability of the meta-analysis.

Another important finding of the present review is that 5 studies showed a reduction in the length of stay on the ventilator in the group in which probiotics were administered. It has been shown that treatment with probiotics reduces colonization with pathogenic bacteria in both the oropharynx and the stomach in mechanically ventilated patients. Alexandre et al.[44] from 2014 also confirmed our findings by attributing this effect of probiotic treatment to the effect on the immune system through the effect on mucosa-associated lymphoid tissue, lymphoid tissue in the bronchi and lymphoid tissue in the gut.

In addition, 9 studies showed that treatment with probiotics shortened the length of stay in the intensive care unit and one study showed that the length of hospital stay was also shortened. Some previous studies with similar results attributed this to the ability of lactobacilli to degrade arginine to nitric oxide, which is involved in several important gastrointestinal functions, such as bacteriostasis, mucus secretion, regulation of motility and visceral blood flow, and stimulation of immune functions of the gastrointestinal system.[45] In our review, 2 studies showed a statistically significant reduction in episodes of diarrhea and

their duration in days. Our finding is consistent with previous systematic reviews that have also shown that probiotics can reduce the incidence of antibiotic- and Clostridium difficile-associated diarrhea[46] and the same was shown to a recent review.[41] The secondary results were also interesting. Probiotics alone had a better effect than synbiotics and microbial doses of ≥5 billion colony-forming units (CFU) per day and duration of probiotic therapy of at least 14 days or longer were associated with statistically significant results. Both results need to be considered and reviewed to see if they can be verified in future studies. Finally, it should be mentioned that 6 out of 7 RCTs that reported on the safety of probiotic administration found no adverse effects associated with probiotics. Although one recent RCT found that the same percentage (1.1%) of the group receiving probiotics and of the group receiving placebo had adverse events, thus safety should be better investigated. A more recent review also showed that probiotics had higher adverse events than control.[47] Administration of probiotics to critically ill patients should be assessed in many well-designed new clinical trials, so that their positive results can be verified many times over and clear guidelines for their effective administration will be established.

Limitations

However, like any systematic review, this study has several limitations. First, the population was heterogeneous and included general ICU patients, surgical ICU patients, patients with multiple injuries, patients with head injuries, etc. In addition, there were many different exclusion criteria in each clinical trial such as immunosuppression, malignancies, prior antibiotic use, liver, gastroenterological and respiratory diseases. The type of intervention in each study varied in terms of the strains administered, their combinations, their dosage and the duration of administration. Finally, the degree of quality of the studies also varied, with some meeting all criteria to the maximum, such as double-blind study, computer randomization, detailed description of subjects who were rejected or dropped out of the study and some others without any randomization, which did not include the exact type of randomization and were qualitatively weak.

Conclusions and recommendations

Our systematic review found that probiotics reduce infectious complications, including ventilator-associated pneumonia, in critically ill patients and positively influence ICU and hospital LOS, days on MV and diarrhea. Furthermore, probiotics seemed to have better effect than synbiotics and microbial doses of ≥5 billion colony-forming units (CFU) per day and duration of probiotic therapy of at least 14 days or longer were associated with statistically significant results. However, clinical heterogeneity and potential publication bias limit a clear clinical recommendation. Further research on probiotics in critically ill patients and more high-quality clinical trials are needed to demonstrate these benefits.

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ANNEX

TABLE 1. Randomized studies evaluating probiotics in critically ill patients.

	Authors/ Year	Country	Study Design	Quality Score	Participants intervention vs control	Modalities of treatment administration	Intervention/ Dose/ Duration	Control	Primary outcome
1	**Jain et al, 2004 (11)**	Germany	SC, RCT, DB (SYN)	5	90 ICU patients (45 intervention/ 45 control)	Btd through NGT	Trevis capsule (Chr Hansen), 3/d 4_10^9 CFU L. acidophilus La5, B. lactis Bb-12, S. thermophilus and L. bulgaricus + Oligofructose (7.5 g Raftilose powder, 2/d) for 10d	NR	Incidence and nature of gastric colonization
2	**Arruda et Aguilar-Nascimento, 2004 (12)**	Brazil	SC, RCT, DB (PRO)	5	20 ICU patients (10 intervention / 10 control)	Btd through NGT	Polymeric diet with 30 g of glutamine and 240 ml of fermented milk with the probiotic strain Lactobacillus johnsoni (La 1) 10^9 (LC1®, Nestle, Sao Paulo, Brazil), 5 to 14 d	Polymeric Diet	Incidence of ICU acquired infections, LOS in ICU & duration of MCV
3	**Klarin et al, 2005 (13)**	Sweden	SC, RCT, SB (PRO)	3	17 ICU patients on antibiotics (9 intervention / 8 control)	Btd through NGT	Fermented oatmeal formula containing 10^9 CFU Lp 299v (Probi AB, Lund, Sweden) 50 ml every 6 h × 3 days then 25 ml every 6 h until ICU discharge	EN (Impact or Nutrodrip fiber). Some patients needed PN	Lp 299v survival through the passage from the stomach to the rectum
4	**McNaught et al, 2005 (8)**	United Kingdom	SC, RCT Open label (PRO)	3	103 ICU patients (52 interventions / 51 control)	Btd through Oral, NJT	EN or PN + Proviva, (oatmeal and fruit drink) 5 × 10^7 CFU/ml of L. plantarum 299 v × 500 mls until hospital discharge or beyond	EN or PN alone	Systemic inflammatory response
5	**Kotzampassi et al, 2006 (14)**	Greece	MC, RCT,DB (SYN)	5	65 severe multiple trauma ICU patients (35 intervention /30 control)	Btd through GT or NGT	Synbiotic 2000Forte, Medipharm, Sweden, (10^{11} CFU, Pediococcus pentoseceus, Leuconostoc mesenteroides, L. paracasei ssp 19,	The placebo preparation consisted of identical doses of powdered	Systemic infection rate (SIRS and MODS) and Mortality

							and L. plantarum 2362), 1 sachet/d + 2.5 g inulin, oat bran,pectin, and resistant starch.for 15 days diluted in 100 ml of tap water.	glucose polymer (maltodextrin, Caloreen, Nestle, UK).	
6	**Spindler et al, 2007 (15)**	Slovenia	SC, RCT, Open label (SYN)	2	113 multiple trauma ICU patients receiving MV>4d (26 intervention /87 control)	Btd through NGT	Synbiotic 2000; Medipharm Sweden, (10^{10} *CFU of Pediococcus pentosaceus, Lactococcus raffinolactis , Lactobacillus paracasei* 19, *Lactobacillus plantarum*)once a day diluted in 100 ml of lukewarm sterile water until ICU discharged or death	3 different formulas of enteral feeding	Incidence of ICU acquired infections
7	**Knight et al, 2009 (16)**	United Kingdom	SC, RCT, DB (SYN)	5	259 general ICU patients requiring MV for>48 h (130 intervention / 129 control)	Btd through NGT or OGT	Synbiotic 2000Forte, Medipharm, Sweden, (at a dose of 10^{10} bacteria per sachet, twice a day + Betaglucan, Inulin, Pectin and Resistant starch (2.5 g of each as prebiotics diluted in 50–100 ml of sterile water for 28 d or ICU discharge or death Incidence	A crystalline cellulose-based placebo twice a day	Incidence of VAP
8	**Giamarellos-Bourboulis et al, 2009 (17)**	Greece	MC, RCT, DB (SYN)	3	72 multiple trauma ICU patients (36 intervention / 36 control)	Btd through GT or NGT	Synbiotic 2000 Forte, Medipharm, Sweden, (10^{11} CFU) for 15 days diluted in 100 ml of tap water	NR	Incidence of ICU acquired infections and VAP
9	**Morrow et al, 2010 (18)**	United States	SC, RCT, DB (PRO)	5	138 general ICU patients (68 intervention / 70 control)	Btd through Oropharynx and NGT	EN (routine care) + Lactobacillus rhamnosus GG, 2 × 10^9 BID aslubricant and mixed with water until extubation	EN (routine care) + inert plant starch inulin (prebiotic) BID as lubricant and mixed with water	Incidence of VAP

10	**Frohmader et al, 2010 (19)**	Australia	SC, RCT, DB (SYN)	5	45 General ICU patients on antibiotics (20 intervention / 25 control)	Btd through NGT or NJT	EN (Standard) + VSL #3 (VSL Pharmaceuticals, Gaithersburg, Maryland, 450 10^9 CFU *Bifidobacterium breve, Bifidobacterium longum* (>10x10^9/g), *Bifidobacterium infantis* (>10x10^9/g), *L acidophilus, Lactobacillus plantarum, Lactobacillus casei, L bulgaricus, Streptococcus thermophilus* (>100 x 10^9/g) mixed in 50ml nutritional supplement (Sustagen), twice daily until hospital discharge	EN (Standard) + placebo mixed in 50ml nutritional supplement (Sustagen), twice daily until hospital discharge	Number of episodes of liquid stool in enteral fed patients
11	**Barraud et al, 2010 (20)**	France	SC, RCT, DB (PRO)	5	167 Mechanically ventilated ICU patients (87 intervention / 80 control)	Btd through NGT	EN (Fresubin) + capsule 2 * 10^{10} of revivable bacteria (Lactobacillus rhamnosus GG, Lactobacillus casei, Lactobacillus acidophilus,and Bifidobacterium bifidum) + potato starch (Nutergia, Capdenac, France) 5 capsules/day diluted in 20 mL of water for 28 days	EN (Fresubin) + placebo capsules (excipient of potato starch) 5 capsules/day diluted in 20 mL of water for 28 days	Assess the effects of prophylactic probiotic administration in patients ventilated for up to 2 days
12	**Tan et al, 2011 (21)**	China	SC, RCT, SB (PRO)	3	52 ICU patients with closed head injury (26 intervention / 26 control)	Btd through NGT	EN (standard), total of 10^9 bacteria i.e., 7 sachets each 0.5 × 10^8 Bifidobacterium longum, 0.5 × 10^7 Lactobacillus bulgaricus and 0.5 × 10^7Streptococcus thermophilus for 21 days dissolved in 20 ml sterilized distilled water	EN (Standard)	Assess the effects of probiotics to the Th1/Th2 imbalance and clinical outcomes in TBI patients

13	**Ferrie et al, 2011 (22)**	Australia	SC, RCT, DB (PRO)	5	36 ICU patients enterally fed adults with diarrhea (18 intervention / 18 control)	Btd through OGT	EN (Standard) + Culturelle (Lactobacillus rhamnosus GG), 10^{10} species/capsule +280 mg inulin powder for 7 days, diluted in 50 mL sterile water	EN (Standard) + Raftiline, gelatin capsule with 280 mg inulin powder (prebiotic) for 7 days, diluted in 50 mL sterile water diluted in 50 mL sterile water	Duration of diarrhea
14	**Malik et al, 2016 (23)**	Malaysia	SC, RCT, DB (PRO)	5	60 ICU patients (30 intervention / 30 control)	Btd through NGT	3gr granule of $30*10^9$ CFU of Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidum, Bifidobacterium longum and Bifidobacterium infantis diluted in 5mL twice a day for 7 days	3gr Granule diluted in 5mL twice a day for 7 days	Duration until returning to normal gut function
15	**Zeng et al, 2016 (7)**	China	MC, RCT, Open label (PRO)	3	235 ICU patients (117 intervention / 118 control)	Btd through NGT	1 capsule (Medilac-S, China) 0.5 g three times daily. Each probiotic capsule contained active Bacillus subtilis and Enterococcus faecalis at a concentration of 4.5 × 10^9 /0.25 g and 0.5 × 10^9/0.25 g, Respectively for 14 days	EN (standard)	Preventive effect of probiotics on VAP
16	**Shimizu et al, 2018 (24)**	Japan	MC, RCT, SB (SYN)	3	72 ICU septic patients (35 intervention / 37 control)	Btd through NGT	The probiotics used were Yakult BL Seichoyaku (Yakult Honsha, Tokyo, Japan), 1 × 10^8 CFU B. breve /g and 1 × 10^8 CFU L. casei /g + prebiotics	NR	Incidence of ICU acquired infections and VAP and gut microbiota modulation

							3g/d galactooligo-saccharides & 10g/d galactooligo-saccharides (Oligo-mate S-HP, Yakult Honsha) were used as SYNbiotic therapy until oral in-take was initiated or 4 weeks		
17	**Mahmoodpoor et al, 2019 (25)**	Iran	MC, RCT, DB (PRO)	5	100 ICU patients (48 intervention / 52 control)	Btd through NGT	1 capsule of 10^{10} CBU of *Lactobacillus* species (*casei*, *acidophilus*, *rhamnosus*, *bulgaricus*), *Bifidobacterium* species (*breve*, *longum*) and *Streptococcus thermophilus*. (Lactocare, Zist-Takhmir, Tehran, Iran) twice a day for 14d	Placebo capsule contained sterile starch powder, visually identical twice a day for 14d	Incidence of VAP
18	**Tsaousi et al, 2019 (26)**	Greece	SC, RCT, SB (PRO)	3	58 ICU multi-trauma patients, requiring mechanical ventilation for >10 days. (28 intervention / 30 placebo)	Btd through NGT or OGT	A four-probiotic formula was applied and each patient received two capsules per day from Day1 to Day 15 post ICU admission. The content of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubricant. The follow-up period was 30 days	Placebo	Positive effect on the incidence of VAP or other ICU-acquired infections and ICU stay in critically ill multi-trauma patients.
19	**Habib et al, 2020 (27)**	Egypt	SC, RCT, DB (PRO)	4	65 adult multiple trauma patients on mechanical ventilator (expected ≥48 h) (32 intervention / 33 placebo)	Btd through NGT or OGT	32 patients received one Lacteo Forte® sachet (Lactobacillus delbrueckii and Lactobacillus fermentum ($10 * 10^9$), 3 times daily during their ICU stay	33 Patients received similar regimen of placebo sachets	Evaluate the role of probiotics in prophylaxis of VAP after multiple trauma.

20	**Nazari et al, 2020 (28)**	Iran	MC, RCT, SB (SYN)	4	147 Neurosurgical ICU patients on mechanical ventilator ≥48 h (73 intervention / 74 placebo)	Btd through NGT	2 Daily Lactocare capsules (Zist Takmir Company Terhan -Iran) with 20cc distilled water twice a day	2 Starch capsules with 20cc distilled water twice a day	The effects of probiotics on the prevalence of VAP in multi-trauma patients in neurosurgical ICU
21	**Wang et al, 2021 (29)**	China	SC, RCT, SB (PRO)	4	61 Respiratory ICU patients (28 intervention / 33 placebo)	Btd orally or through NGT or OGT	One tablet MIYA-BM® (Miyarisan pharmaceutical Co., Ltd., Tokyo, Japan), contains Clostridium butyricum at 10^6 CFU bacteria per sachet) was administered thrice daily	A placebo tablet was administered thrice daily	Whether exogenous probiotics could improve the intestinal barrier function effect via attenuating inflammation and immunomodulation to improve the clinical outcomes in critically ill patients.
22	**Litton et al, 2021 (30)**	Australia	MC, RCT, DB (PRO)	5	228 ICU patients (110 intervention / 108 placebo)	Btd through NGT or OGT	The study drug (contained 2×10^{10} colony-forming units (CFUs) of L. plantarum 299v per capsule) was administered once daily, for 60 days	The placebo patients received an identical capsule containing microcrystalline cellulose	Whether early and sustained L. plantarum 299v therapy administered to adult ICU patients increased days alive and at home.
23	**Johnstone et al, 2021 (31)**	Canada, USA and Saudi Arabia	MC, RCT, DB (PRO)	4	2650 ICU patients ≥18 years old, anticipated to be mechanically ventilated ≥72 hours	Btd through NGT or OGT	One capsule, 1×10^{10} colony forming units of L. rhamnosus GG (i-Health, Inc.) in suspended in tap water or sterile water (depend-	Patients in the placebo group receive an identical capsule containing	Development of VAP

					(1318 intervention / 1332 Placebo)		ent on local practices), administered through a nasogastric or orogastric feeding tube up to 60 days or until discharge from the ICU.	microcrystalline cellulose.	
24	**Tsilika et al, 2022 (32)**	Greece	MC, RCT, DB (PRO)	4	112 multi-trauma patients, expected to require mechanical ventilation for >10 days (59 intervention / 53 Placebo)	Btd through NGT or OGT	2 sachets twice daily for 15 days (Lactobacillus acidophilus LA-5 [1.75 × 10^9 colony-forming units (CFU)], Lactobacillus plantarum (0.5 × 10^9 CFU), Bifidobacterium lactis BB12 (1.75 ×10^9 CFU) and Saccharomyces boulardii (1.5 × 10^9 CFU) twice daily for 15 days		The aim of this study was to assess the efficacy of a probiotic regimen for VAP prophylaxis in mechanically ventilated multi-trauma patients
25	**Lu et al, 2024 (33)**	China	SC, RCT, DB (PRO)	5	24 ICU patients ≥18 years old, anticipated to be mechanically ventilated ≥72 hours (12 intervention / 12 Placebo)		The probiotic group was given Bifco (Shanghai Shinji Pharmaceutical Factory Co., Ltd., Sinopharm quasizu s10950032, specification: 210 mg/grain) twice daily until leaving the ICU	The control group received conventional treatment only	The effect of mixed probiotics on the diversity of the pulmonary fora in critically ill patients requiring mechanical ventilation by analyzing the changes in lung microbes

Notes: SC=single center, MC=multi center, ICU= intensive care unit, DB= double blind, RCT=randomized controlled trial, SYN = synbiotics, PRO =probiotics, PRE=prebiotics, NGT= nasogastric tube, GT= gastrostomy tube, MV=mechanical ventilation, OGT= orogastric tube, CFU=colony forming units, VAP= ventilator-associated pneumonia, BID= twice daily

TABLE 2. Reported clinical outcomes in RCTs evaluating probiotics in critically ill patients.

	Authors/ Year	**ICU Mortality** Control vs Intervention	**Hospital Mortality** Control vs Intervention	**Incidence of ICU-Acquired Infections** Control vs Intervention	**Incidence of ICU-Acquired Pneumonia** Control vs Intervention	**Duration of Mechanical Ventilation** (days) Control vs Intervention	**ICU LOS** (days) Control vs Intervention	**Hospital LOS** (days) Control vs Intervention	**Diarrhea** (days) Control vs Intervention
1	**Jain et al, 2004** (11)	NR	22/45 (49%) vs 20/45 (45%)	26/45 (58%) vs 33/45 (73%)	NR	NR	5 (3–14) vs 7 (3–16)	15 (9–26) vs 14 (9–29)	NR
2	**Arruda et Aguilar-Nascimento ,2004** (12)	0	NR	10 (100 %) vs 5 (50 %) (p=0.03)	NR	14 (3–53) vs 7 (1–15) (p=0.04)	22 (7–57) vs 10 (5–20) (p<0.01)	NR	NR
3	**Klarin et al, 2005** (13)	2/7 (29% vs 1/8 (12%)	2/7 (29%) vs 2/8 (25%)	NR	NR	17 (13–28) vs 12 (7–20)	16.3 ± 15.7 vs 14.2 ± 10.6	34.3 ± 15.4 vs 48.3 ± 30.4	NR
4	**McNaught et al, 2005** (8)	18/51 (35%) vs 18/52 (35%)	NR	Septic morbidity 22/51(43%) vs 21/52 (40%)	NR	NR	4 (2–7) vs 5 (2–9)	NR	NR
5	**Kotzampassi et al, 2006** (14)	9/30 (30%) vs 5/35 (14.3%)	NR	90% vs 63% (p = 0.01)	NR	26 (7–60) vs 15 (5–32) (p = 0.001)	43 (17–82) vs 25 (13–54) (p= 0.01)	NR	NR
6	**Spindler et al, 2007** (15)	5/87 (6%) vs 2/26 (8%)	NR	46/87 (53%) vs 5/26 (19%) (p =0.003)	46/87 (53%) vs 5/26 (19%) (p =0.032)	34/87 (39%) vs 4/26 (15%)	NR	NR	NR
7	**Knight et al, 2009** (16)	34/129 (26%) vs 28/130 (22%)	42/129 (33%) vs 35/130 (27%)	NR	17/129 (13%) vs 12/130 (9%)	5 (3-11) vs 5 (2-9)	7 (3-14) vs 6 (3-11)	18 (7-32) vs 19 (8-36)	
8	**Giamarellos-Bourboulis et al, 2009** (17)	10/36 (27.8%) vs 5/36 (13.9%)	NR	90% vs 63% (p= 0.01)	12 (33.3%) vs 5 (13.9%) (p=0.047)	29.7 vs 16.7 (p=0.001)	41.3 vs 27.2 (p= 0.01)	NR	NR
9	**Morrow et al, 2010** (18)	21.4% vs 17.6%	NR	NR	33 (45.2%) vs 17 (23.3%) (p=0.005)	9.6 ± 7.2 vs 9.5 ±6.3	14.6 ±11.6 vs 14.8 ±11.8	21.7 ±17.4 vs 21.4± 14.9	Non C. difficile diarrhea 44 (62.9%) vs 42 (61.8%) C. difficile diarrhea,

									9.8± 4.9 vs 13.2 ±7.4, ICU-associated diarrhea 5.9 ±3.8 vs 4.1 ± 3.7, (p=0.03)
10	**Frohmader et al, 2010** **(19)**	3/25 (12%) vs 5/20 (25%)	NR	NR	NR	NR	8.1 ± 4 vs 7.3 ± 5.7	NR	Diarrhea episodes/ pt/day 1.05± 1.08 vs 0.53 ± 0.54 (p=0.03)
11	**Barraud et al, 2010** **(20)**	21 (26.2%) vs 21 (24.1%)	NR	30 (37.5%) vs 30 (34.4%)	15 (18.7%) vs 23 (26.4%)	NR	20.2 ± 20.8 vs 18.7 ± 12.4	28.9 ± 26.4 vs 26.6 ± 22.3	42 (52.5%) vs 48 (55.2 %)
12	**Tan et al, 2011** **(21)**	28 days 5/26 (19%) vs 28 days 3/26 (12%)	NR	15/26 (58%) vs 9/26 (35%)	13/26 (50%) vs 7/26 (27%)	NR	10.7 ± 7.3 vs 6.8 ± 3.8 (p=0.034)	NR	NR
13	**Ferrie et al, 2011** **(22)**	NR	2/18 (11%) vs 2/18 (11%)	16/18 (89%) vs 14/18 (78%)	NR	NR	29.75 ± 18.81 vs 32.04 ± 24.46	59.04 ± 33.92 vs 54.50 ± 31.26	2.56 ± 1.85) vs 3.83 ± 2.39
14	**Malik et al, 2016** **(23)**	NR	NR	NR	NR	14.0(±8.0) vs 8.4(±3.5) (p<0.01)	15.8(±7.8) vs 10.9(±3.9) (p<0.01)	NR	NR
15	**Zeng et al, 2016** **(7)**	9/117 (7.7 %) vs 15/118 (12.7 %)	16/108 (14.8 %) vs 11/103 (10.7 %)	NR	59/117 (50.4%) vs 43/118 (36.4%) (P = 0.031)	17 (13–28) vs 12 (7–20)	22 (11–56) vs 18 (14–32)	10.6 ± 10.2 vs 13.5 ± 12.4	NR
16	**Shimizu et al, 2018** **(24)**	4 (10.8%) vs 3 (8.6%)	NR	25 (67.6%) vs 10 (28.6%) (p< 0.05)	18 (48.6%) vs 5 (14.3%) (p< 0.05)	NR	28 (17–45) vs 23 (13–43)	NR	NR
17	**Mahmoodpoor et al, 2019** **(25)**	6 (11.1%) vs 5 (10.4%)	NR	NR	0.94 vs 0.66 (p=0.04)	290 ± 171 vs 210 ± 115 (p=0.02)	18.6 ± 6.3 vs 11.6 ± 8 (p< 0.07)	21.1 ± 5.7 vs 14.2 ± 8.6 (p< 0.02)	15 (27.8) vs 7 (14.6%) (p=0.08)
18	**Tsaousi et al, 2019** **(26)**	30-day mortality 6.78% vs	NR	NR	53.3% vs 32.1% (p=0.001)	NR	ICU stay > 30 days 401%	NR	NR

		10.7%					vs 7.1% (p=0.002)		
19	**Habib et al, 2020 (27)**	12 (36.36%) vs 11 (34.38%)	NR	NR	7 (21.21%) vs 5 (15.63%)	9.10±3.642 vs 11.60±4.775	12.63±3.681 vs 14.60±4.775	NR	NR
20	**Nazari et al, 2020 (28)**	NR	NR	NR	33 (44.59%) vs 9 (12.32%) (p=0.001)	8.00+01.51 vs 8.19+01.21	14.88+01.79 vs 13.35+01.45	NR	NR
21	**Wang et al, 2021 (29)**	21.43% Vs 21.21%	NR	NR	NR	NR	12.94 vs 4.85 (p=0.00)	19 (14- 26) vs 19 (12.5 - 28.5)	66.67% vs. 60.71%
22	**Litton et al, 2021 (30)**	4 (3.7%) vs 4 (3.6%)	4 (3.7%) vs 5 (4.6%)	5 (4.6%) vs 8 (7.3%)	NR	NR	NR	NR	NR
23	**Johnstone et al, 2021 (31)**	296 (22,2%) vs 279 (21.2%)	381 (28.6%) vs 363 (27.5%)	418 (31.4%) vs 414 (31.4%)	284 (21.3%) vs 289 (21.9%)	7 (4-13) vs 7 (4-13)	12 (8-18) vs 12 (7-19)	22 (13-40) vs 22 (13-42)	787 (59.1%) Vs 785 (59.6%)
24	**Tsilika et al, 2022 (32)**	NR	NR	NR	15 (28.3) vs 7 (11.9) (p=0.034)	NR	(11-28) vs (8-28) (p=0.01)	(11-28) vs (12-27) (p=0.08)	2 (3.8%) Vs 0
25	**Lu et al, 2024 (33)**	28-day mortality rate 4 (33.33%) vs 2 (16.67%)	NR	NR	1 vs 0	11.75±6.283 vs 10.92±4.209	NR	NR	NR

Notes: vs=versus, NR=not reported, p=p-value, C. difficile = Clostridium difficile
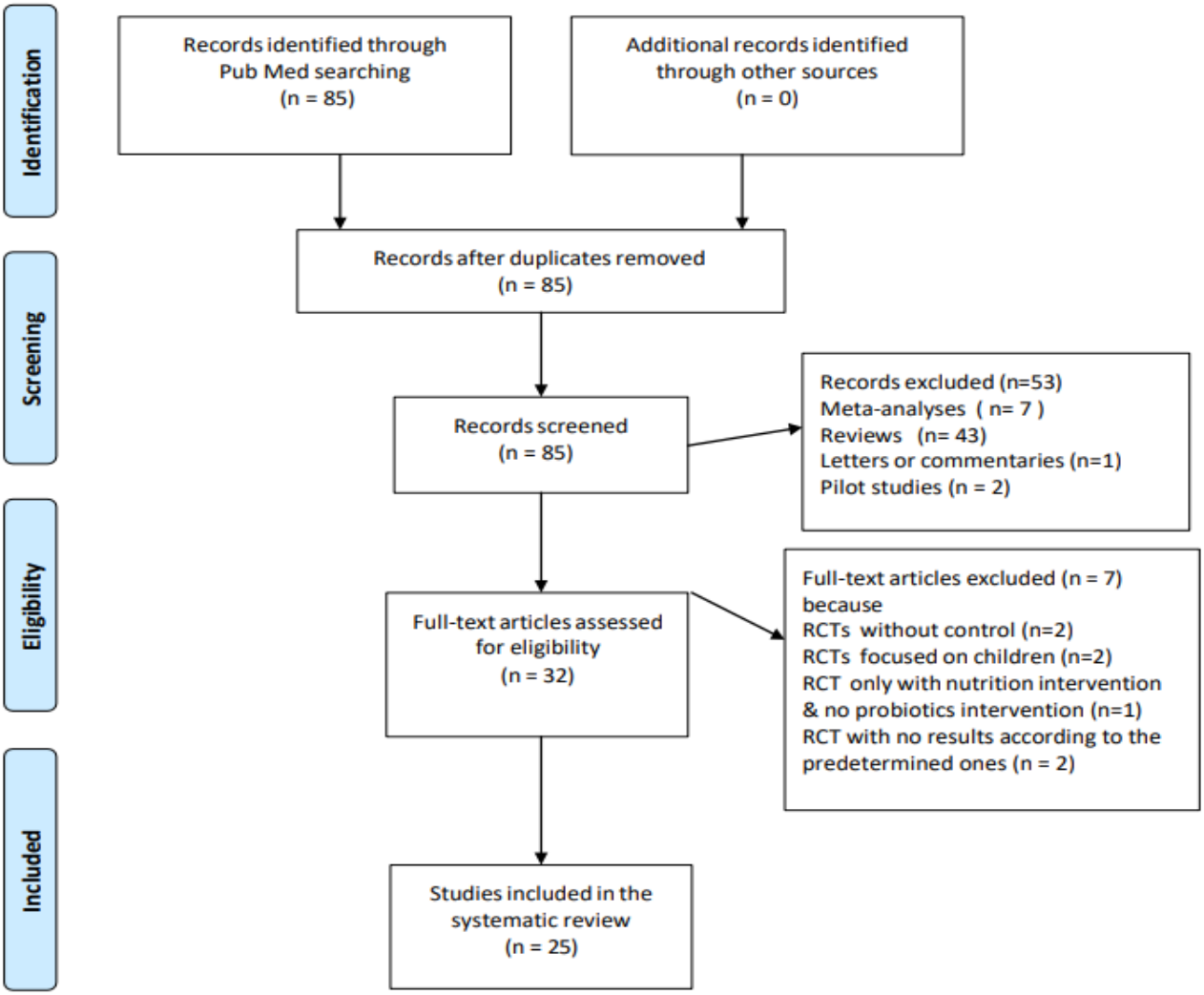
Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. RCT= Randomized Controlled Trial.