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Synbiotic Therapy Prevents Nosocomial Infection in Critically Ill Adult Patients: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials Based on a Bayesian Framework

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Background: The efficacy of synbiotics, probiotics, prebiotics, enteral nutrition or adjuvant peripheral parenteral nutrition (EPN) and total parenteral nutrition (TPN) in preventing nosocomial infection (NI) in critically ill adults has been questioned. We conducted a systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) to evaluate and rank the effectiveness of these therapies on NI amongst critically ill adults.

Methods: Four electronic databases were systematically searched up to June 30, 2019 for RCTs comparing the administration of probiotics, prebiotics, synbiotics, EPN and TPN in critically ill adults. The primary outcome was NI. The relative efficacy of all outcomes was determined by a Bayesian framework with random effects NMA. We estimated the odds ratio (OR) and mean difference (MD) and ranked the comparative effects of all regimens with the surface under the cumulative ranking probabilities. The study has been registered on PROSPERO (CRD42019147032).

Results: Fifty-five RCTs (7,119 patients) were identified. Primary outcome showed that synbiotics had the best effect in preventing NI than EPN (OR 0.37; 95% CrI 0.22–0.61), probiotics followed (OR 0.52; 95% CrI 0.34–0.77), whereas TPN significantly increased NI (OR 2.29; 95% CrI 1.48–3.67). Subgroup analysis showed that TPN significantly increased NI in intensive care unit (ICU) patients (OR 1.57; 95% CrI 1.01–2.56) and severe acute pancreatitis (SAP) patients (OR 3.93; 95% CrI 1.74–9.15). Secondary outcomes showed that synbiotics were more effective in preventing hospital-acquired pneumonia (HAP) (OR 0.34; 95% CrI 0.11–0.85), catheter-related bloodstream infection (OR 0.08;

95% CrI 0.01–0.80), urinary tract infection (OR 0.27; 95% CrI 0.08–0.71) and sepsis (OR 0.34; 95% CrI 0.16–0.70) than EPN. Amongst the treatments, probiotics were most effective for shortening the mechanical ventilation duration (MD −3.93; 95% CrI −7.98 to −0.02), prebiotics were most effective for preventing diarrhea (OR 0.24; 95% CrI 0.05–0.94) and TPN was the least effective in shortening hospital length of stay (MD 4.23; 95% CrI 0.97–7.33).

Conclusions: Amongst the five therapies, synbiotics not only prevented NI in critically ill adults but also demonstrated the best treatment results. By contrast, TPN did not prevent NI and ranked last, especially in ICU and SAP patients.

Take-Home Message: Nosocomial infection is a leading cause of mortality in critically ill patients in the ICU. However, the efficacy of synbiotics, probiotics, prebiotics, enteral nutrition or adjuvant peripheral parenteral nutrition and total parenteral nutrition in preventing nosocomial infection in critically ill adults has been questioned. The network meta-analysis provides evidence that amongst the five therapies, synbiotics not only prevented NI in critically ill adults but also demonstrated the best treatment results. By contrast, TPN did not prevent NI and ranked last, especially in ICU and SAP patients. The results of this study will provide a new scientific basis and a new idea for the debate on the efficacy of synbiotics and other treatments in the improvement of prognosis in critically ill adult patients.

Tweet: Synbiotic prevents nosocomial infection in critically ill adults, while total parenteral nutrition has the adverse curative.

Keywords: critical illness, synbiotic, nosocomial infection, network meta-analysis, Bayesian

INTRODUCTION

Nosocomial infection (NI) is a common and serious complication in patients with critical illness (1, 2). Patients admitted to the intensive care unit (ICU) are especially susceptible to NI because of their critical illnesses and conditions, such as mechanical ventilation (MV) (3), intracranial hemorrhage (1), severe trauma, severe acute pancreatitis (SAP), complex surgery (2), and extracorporeal membrane oxygenation (ECMO) (4). Intestinal microbiota dysbiosis suggested that gastrointestinal dysfunction plays an important role in the pathogenesis of NI in critically ill patients (5–9). It can result in an increase in susceptibility to NI and significantly affect clinical outcomes (10–15).

Probiotics are live microorganisms that exert beneficial effects by protecting against pathogens, improving intestinal barrier function and inducing host immunomodulation (16). Prebiotics are a substrate that are selectively utilized by host microorganisms maintaining gut homeostasis and improving health outcomes (17–23). Enteral nutrition or adjuvant peripheral parenteral nutrition (EPN) and total parenteral nutrition (TPN) have the functions of protecting the intestinal barrier and providing adequate nutrient substrates, respectively (24). Therefore, all above therapies can partially improve intestinal microbiota dysbiosis, and are widely used in the treatment of NI in critically ill adults (17, 25).

Nonetheless, the advantages of probiotics, prebiotics, synbiotics, EPN and TPN on preventing NI in critically ill patients have been a topic of major debate. Majority of randomized controlled trials (RCTs) performed in critically ill adults have failed to show significant improvement in NI with probiotics, prebiotics and synbiotics therapies (26–34) or have even showed an increased risk of mortality (35). Moreover, RCTs have highlighted the higher risk of bacteremia and fungemia infection resulting from probiotics and synbiotics in immuno-compromised critical patients (33, 35–37).

Many previous conventional meta-analyses have already examined the risks and benefits of probiotics or synbiotics compared with EPN in critically ill adults (38–42). However,

Abbreviations: BSIs, bloodstream infection; CENTRAL, Cochrane Central Register for Controlled Trials; CFU, Colony-forming units; CRBSI, Catheter-related bloodstream infection; CrI, Credible interval; DB, Double-blind; ECMO, Extracorporeal membrane oxygenation; EN, Enteral nutrition; EPN, Enteral nutrition or adjuvant peripheral parenteral nutrition; GCS, Glasgow coma scale; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; HAP; Hospital acquired pneumonia; ICU, Intensive care unit; LOS, Length of stay; MC, Multi-center; MD, Mean difference; MV, Mechanical ventilation; NI, Nosocomial infection; NMA, Network meta-analysis; NR, Not reported; OP, Open study; OR, Odds ratio; PN, Parenteral nutrition; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses; PROSPERO, Prospective register of systematic reviews; RCTs, Randomized controlled trial studies; RR, Risk ratio; SAP, severe acute pancreatitis; SB, Single-blind; SC, single-center; SD, Standard deviation; SUCRA, Surface under the cumulative ranking curve; TPN, Total parenteral nutrition; UTI, Urinary tract infection; VAP, Ventilator-associated pneumonia.

all these meta-analyses were restricted to pairwise comparisons, and only the pooled risk ratio (RR) or odds ratio (OR) were calculated. There was heterogeneity between the included trials, and the relative merit of candidate therapies could not be informed through a direct comparison. Network meta-analyses (NMAs) can not only address this limitation but also improve precision by combining direct and indirect estimates (43). Therefore, this systematic review and NMA aimed to evaluate and rank probiotics, prebiotics, synbiotics, EPN and TPN to determine their effects on improving NI of critically ill adult patients. The results of this study will provide a new scientific basis for the debate on the efficacy of synbiotics and other treatments in the improvement of prognosis in critically ill adult patients.

METHODS

Approval

This literature was written according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) Statement Extension Statement (44). This study was registered on the international prospective register of systematic reviews (PROSPERO CRD42019147032).

Inclusion Criteria

Participants: critically ill patients (≥16 years). If the study population was unclear, we considered a mortality rate higher than 5% in the control group to be consistent with critical illness (42). Interventions: probiotics, prebiotics, synbiotics, EPN and TPN. Primary outcome: NI. Secondary outcomes: hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), bloodstream infections (BSIs), catheter-related bloodstream infection (CRBSI), urinary tract infection (UTI), sepsis, diarrhea, ICU and hospital mortality, ICU and hospital LOS and duration of MV. Study design: RCT.

Exclusion Criteria

The trial did not report outcome variables. The trial was a duplicate publication.

Search Strategy and Study Selection

We conducted a systematic literature search for clinical trials in Pubmed, Embase, Cochrane (CENTRAL) and Web of Science electronic medical databases until June 30, 2019. There was no language restriction. The specific search terms were used for each database, and the details of the search strategy were modified with a combination of relevant terms as proposed by Cochrane for systematic reviews of RCTs (45). The following MeSH terms were used to search for relevant literature: "critically ill" OR "synbiotic" OR "probiotic" OR "prebiotic" OR "enteral nutrition" OR "parenteral nutrition" OR "nosocomial infection" combined with RCTs.

Five reviewers selected studies for inclusion by screening the titles and abstracts of the literature independently. Thereafter, they reviewed the full texts carefully according to the inclusion and exclusion criteria to determine the final inclusion of articles. Any discrepancies between reviewers were resolved by a consensus after a discussion with a sixth reviewer.

Definition of Interventions

Probiotics are live microorganisms that may confer health benefits on the host when administered in adequate amounts (16, 17). Prebiotics are substrates that are selectively utilized by host microorganisms and confer a health benefit (16, 18). By contrast, synbiotics are composed of probiotics and prebiotics (**Supplementary File 3**). The US Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) criteria (46) were used to diagnose NI including HAP, VAP, BSIs, CRBSI, UTI, intraabdominal infection, gastroenteritis system infection and surgical site infection (**Supplementary Table 2.3**). We used definitions of diarrhea as defined by the authors in their original articles. From all trials, we combined hospital mortality where reported. If the mortality time frame was not specified as either ICU or hospital, it was presumed to be the latter.

Data Extraction

For duplicate studies, we included only the research with the most informative and complete data. Five investigators extracted independently all the available data from each study. These data included characteristics of study, details of patients enrolled, type and dose of intervention and details of primary and secondary outcomes. Disagreements among the three investigators were resolved by a consensus after discussing with a sixth reviewer.

Assessment of Risk of Bias (ROB) and Quality

We assessed each included studies' ROB in accordance with the Cochrane collaboration risk of bias tool (45). A summary of the ROB was documented as low, unclear or high. Studies were classified as having low ROB if none was rated as high ROB, and three or less were rated as unclear risk. Studies had moderate ROB if one was rated as high ROB or none was rated as high ROB but four or more were rated as unclear risk. All other cases were assumed to pertain to high ROB.

Publication bias was assessed using the comparison-adjusted funnel plots (47, 48).

Additionally, we assessed the certainty of evidence contributing to network estimates with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (high, moderate, low and very low) (49).

Quantitative Data Statistical Analysis

All data were conducted according to the Cochrane Handbook. In pairwise meta-analysis and NMA, dichotomous and continuous variables were analyzed using OR and mean differences (MD), respectively.

The study effect sizes were assessed using a Bayesian framework with a random effects NMA model (50, 51). Dichotomous outcomes used the binomial likelihood, and continuous outcomes used the normal likelihood. Four Markov chains were adopted for initial value setting. The initial update iteration number of the model and the continuous update iteration number were set as 20,000 and 50,000, respectively. The

first 20,000 annealing times were used to eliminate the influence of the initial value, and sampling was started from 20,001 times. The initial and continuous iteration numbers of the model increased if the convergence of models was not satisfactory. A potential scale reduction factor approaching 1 indicated that the model convergence was satisfactory (52).

The treatment for each outcome was ranked by using the surface under the cumulative ranking curve (SUCRA) (53).

Heterogeneity variance was considered to measure the extent of a cross-sectional study and within-comparison variability on treatment effects. $I^2 < 25\%$ and $I^2 > 75\%$ indicate low and high heterogeneity, respectively (54–56). Statistically significant heterogeneity was set at $I^2 > 50\%$, and the sources of heterogeneity were discussed.

A statistical evaluation of inconsistency was assessed by the design-by-treatment test (55, 57) and node splitting

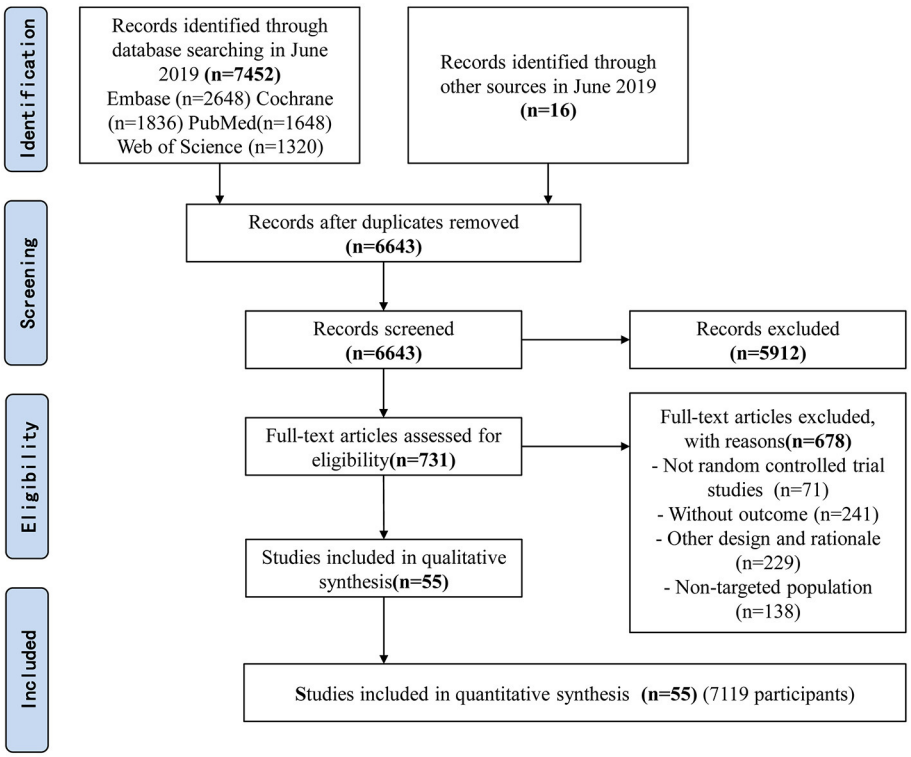

FIGURE 1 | Flow diagram of included studies.

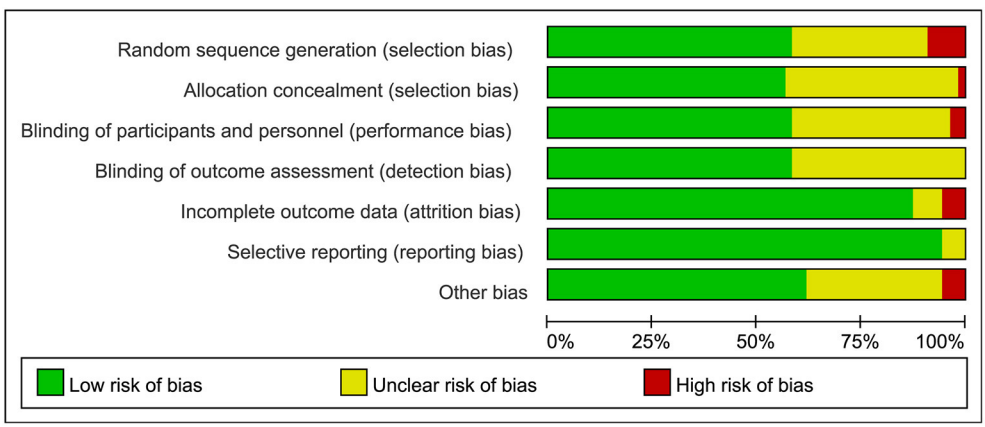

FIGURE 2 | Risk bias assessment graph for included studies.

(52). Inconsistencies were found between direct and indirect comparison evidence when $P < 0.05$.

The transitivity assumption underlying NMA was evaluated by comparing the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons (53, 58).

This study evaluated whether treatment effects for the primary outcome are robust in subgroup analyses by using ICU patients, MV patients, SAP patients, trauma patients, initial time of nutrition therapy, doses, study year, and quality. In view of the fact that European Society for Clinical Nutrition and Metabolism (ESPEN), Society of Critical Care Medicine (SCCM), and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommend that the initial time of early EN therapy is within 48 h (24, 25), we divided the subgroup of initial nutritional therapy into two groups: within 48 h and beyond 48 h. The average number of obligate anaerobes of normal people was around 10 [log10 colony-forming units (CFUs)/g of feces] (59–61). Therefore, we defined the dose of probiotics that was >2 $\times$ 10^{10} CFU per day as high dose and the rest as moderate to low doses.

The sensitivity of our conclusions was evaluated by analyzing only datasets of studies with high quality.

All statistical analyses were performed with Review Manager 5.3, stata (version 14.0) and R software (version 3.6.1). Network plots and comparison-adjusted funnel plots of NMA were drawn by Stata. NMAs of all outcomes were duplicated using the Netmeta 1.1-0 package in R. Bayesian MCMC simulations were performed by means of JAGS software (gemtc 0.8-2 and rjags 4-10 package) in R. Graphs of SUCRA were obtained using the ggplot2 3.2.1 package in R.

RESULTS

Search Results and Characteristics of the Studies

The searches identified 7,468 articles, and 731 potentially eligible articles were retrieved in full text. Overall, 55 RCTs (comprising

	Braga 1995	Kudsk 1996	Bleichner 1997	Falcao 2004	Jain 2004	Lu 2004	Sun 2004	Klarin 2005	McNaught 2005	Morrow 2005	Kotzampassi 2006	Petrov 2006	Spindler-Vesel 2006	Abdulmeguid 2007
A	Unclear	Low	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
B	Unclear	Low	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Unclear	Low	Low	Low	Low
C	Unclear	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
D	Unclear	Low	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
E	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear	High	Low	Low	Low
F	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
G	Low	Low	Low	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low	Low	Low
Q	Moderate	High	High	High	High	High	Moderate	Low	Moderate	Moderate	Low	High	High	High

	Alberda 2007	Casas 2007	Karakan 2007	Olah 2007	Sramek 2007	Besselink 2008	Forestier 2008	Klarin 2008	Doley 2009	Giamarellos-Bourboulis 2009	Knight 2009	Moses 2009	Barraud 2010	Frohmader 2010
A	Unclear	Low	Low	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low
B	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low
C	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low
D	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low
E	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
F	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
G	Unclear	Low	Unclear	Unclear	Unclear	High	High	Low	Unclear	Unclear	Unclear	Low	Low	Low
Q	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	High	High	Moderate	High	High	High	High

	Morrow 2010	Ferrie 2010	Tan 2011	Hayakawa 2012	Malian 2012	Plaudis 2012	Cui 2013	Elke 2013	Tan 2013	Wang 2013	Lopez de Toro 2014	Sanaie 2014	Zhu 2014	Fu 2015
A	Low	Low	Low	High	Unclear	Low	High	Low	Unclear	Low	Unclear	Low	Low	Low
B	Low	Low	Low	Unclear	Unclear	Low	High	Low	Unclear	Low	Unclear	Low	Unclear	Low
C	Low	Low	High	Unclear	Unclear	Low	High	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
D	Low	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low
E	Low	High	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low
F	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low
G	Low	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	Low	Unclear	Low	Low
Q	High	Moderate	Low	Low	Moderate	High	Low	High	Moderate	High	Moderate	High	High	High

	Kim 2015	Rongrungruang 2015	Fan 2016	Malik 2016	ZarinfarN 2016	Zeng 2016	Alberda 2018	Fazilaty 2018	Kooshk 2018	Reiginer 2018	Shimizu 2018	Tuncay 2018	Mahmoodpoor 2019
A	Low	Low	High	Low	Unclear	Unclear	Unclear	Low	High	Low	Low	High	Low
B	Low	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Low
C	Low	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low
D	Low	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low
E	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Unclear
F	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
G	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low
Q	High	High	Low	Moderate	Moderate	Moderate	Moderate	High	Low	High	High	Low	High

FIGURE 3 | Summary of risk bias assessment for included studies. Studies were classified as having low ROB if none was rated as high ROB, and three or less were rated as unclear risk. Studies had moderate ROB if one was rated as high ROB or none was rated as high ROB but four or more were rated as unclear risk. All other cases were assumed to pertain to high ROB. A = Random sequence generation, B = Allocatin concealment, C = Blinding of participants and personnel, D = Bliding of outcomes assessment, E = Incomplete outcome data, F = Selective reporting, G = Other bias, Q = Quality.

TABLE 1 | Description of included studies.

ID	Author	Year	Country	Diseases	Design	*N*	Mean age (SD)	Male (%)	APACHE II Score	SOFA Score	Intervention
1	Braga et al. (62)	1995	Italy	SICU patients undergoing curative surgery for gastric or pancreatic cancer	SC/OP	50	60.3 (7.8)	NR	NR	NR	EN
						27	59.8 (7.1)		NR	NR	TPN
2	Kudsk et al. (63)	1996	America	ICU patients with severe trauma	SC/OP	33	33 (3)	61	NR	NR	EN
						19	35.7 (2.8)	53	NR	NR	TPN
3	Bleichner et al. (64)	1997	France	Critical patients in ICU	MC/DB	64	61.6 (12.3)	70	NR	NR	Probiotics+EN
						64	64.9 (14.1)	72	NR	NR	Placebo+EN
4	Falcão De Arruda and De Aguilar-Nascimento (65)	2004	Brazil	ICU patients with TBI	SC/DB	10	27 (20)	100	NR	NR	Synbiotics+EN
						10	26 (22.22)	90	NR	NR	EN
5	Jain et al. (27)	2004	United of kingdom	Critical patients in ICU	SC/DB	45	72 (11.11)	58	NR	NR	Synbiotics+EN
						45	73 (11.11)	60	NR	NR	Placebo+EN
6	Lu et al. (66)	2004	China	Critical patients with severe burns	SC/DB	20	36.05 (5.16)	85	NR	NR	Synbiotics+EN
						20	37.4 (2.95)	80	NR	NR	Prebiotics+EN
7	Sun et al. (67)	2004	China	Severe acute pancreatitis patients with organ failure	SC/OP	50	46.7 (16.25)	56	NR	NR	EN
						50			NR	NR	TPN
8	Klarin et al. (68)	2005	Sweden	Critical patients in ICU	SC/OP	8	70.9 (34.81)	33	17 (11.9)	NR	Probiotics+EN
						7	57.5 (31.11)	63	19 (16.3)	NR	EN
9	McNaught et al. (28)	2005	United of kingdom	Critical patients in ICU	SC/DB	52	71 (45.93)	63	12 (5.2)	NR	Probiotics+EN
						51	71 (43.7)	51	12 (6.7)	NR	EN
10	Morrow et al. (69)	2005	America	MV patients	SC/DB	19	NR	NR	NR	NR	Probiotics+EN
						21	NR	NR	NR	NR	Placebo+EN
11	Kotzampassi et al. (70)	2006	Greece	SICU patients with severe multiple trauma	MC/DB	35	52.9 (19)	80	19.36 (2.7)	NR	Synbiotics+EN
						30	55.9 (18)	83	19.36 (2.1)	NR	Placebo+EN
12	Petrov et al. (71)	2006	Russia	Severe acute pancreatitis patients with organ failure	SC/OP	35	51 (18.5)	80	12.0 (3.0)	NR	EN
						34	52 (21.5)	71	12.5 (3.7)	NR	TPN
13	Spindler-Vesel et al. (72)	2006	United of kingdom	SICU patients with severe multiple trauma	SC/DB	26	48 (22.59)	78	13.5 (5.6)	NR	Synbiotics+EN
						29	36 (21.48)	NR	14 (5.2)	NR	Prebiotics+EN
						58	35 (20.8)	NR	12 (8.4)	NR	EN
14	Abdulmeguid and Hassan (73)	2007	Greece	MV > 2 days critical patients in ICU	SC/OP	40	NR	NR	NR	NR	EN
						40	NR	NR	NR	NR	TPN
15	Alberda et al. (74)	2007	Canada	ICU patients	SC/DB	10	60.4 (17.9)	50	18.2 (4.2)	NR	Probiotics+EN
						18	64.9 (16.92)	44	15.9 (4.2)	NR	EN
16	Casas et al. (75)	2007	Spain	Severe acute pancreatitis patients with organ failure	SC/OP	11	61.2 (16.6)	77	NR	NR	EN
						11	55.6 (15.6)	77	NR	NR	TPN
17	Karakan et al. (76)	2007	Turkey	Severe acute pancreatitis patients with organ failure	SC/DB	15	47.3 (16.8)	40	9.4 (3.7)	NR	Prebiotics+EN
						15	44.9 (11.2)	53	9.6 (3.8)	NR	EN

(Continued)

TABLE 1 | Continued

ID	Author	Year	Country	Diseases	Design	*N*	Mean age (SD)	Male (%)	APACHE II Score	SOFA Score	Intervention
18	Olah et al. (77)	2007	Ireland	Severe acute pancreatitis patients with organ failure	SC/DB	33	47.5 (43.7)	82	NR	NR	Synbiotics+EN
						29	46.0 (45.19)	17	NR	NR	Prebiotics+EN
19	Sramek et al. (78)	2007	Czech	Critical patients in ICU	SC/OP	15	55 (19.26)	69	24 (4.44)	NR	Synbiotics+EN
						11				NR	Prebiotics+EN
						144	59.0 (15.5)	57	8.4 (4.5)	1.9 (1.6)	EN
20	Besselink et al. (33)	2008	Netherlands	Patients with predicted severe acute pancreatitis	MC/DB	152	60.4 (16.5)	59	8.6(4.4)	2.1(2.0)	Probiotic+EN
						144	59.0 (15.5)	57	8.4(4.5)	1.9(1.6)	EN
21	Forestier et al. (79)	2008	France	Critical patients in ICU	SC/DB	102	60 (54.07)	64	NR	NR	Probiotics+EN
						106	57 (45.93)	76	NR	NR	Placebo+EN
22	Klarin et al. (80)	2008	Sweden	Critical patients in ICU	MC/DB	22	65.5 (44.44)	59	22 (16.3)	NR	Synbiotics+EN
						22	64 (50.37)	59	11 (20)	NR	Prebiotics+EN
23	Doley et al. (81)	2009	India	Severe acute pancreatitis patients with organ failure	SC/OP	25	38.4 (13.8)	NR	≥8	NR	EN
						25	41.1 (11.3)	NR	≥8	NR	TPN
24	Giamarellos-Bourboulis et al. (82)	2009	Greece	SICU patients with severe multiple injuries	MC/DB	36	52.9	NR	19.36	NR	Synbiotics+EN
						36	55.9	NR	19.36	NR	EN
25	Knight et al. (26)	2009	United of kingdom	MV patients	SC/DB	130	49.5 (19.6)	62	17 (8.1)	NR	Synbiotics+EN
						129	50.0 (18.5)	62	17 (7.4)	NR	Placebo+EN
26	Moses et al. (83)	2009	India	ICU patients with acute organophosphate poisoning needing invasive mechanical ventilatory support	SC/OP	29	29.41 (11.8)	76	NR	NR	EN
						30	30.83 (12.4)	73	NR	NR	TPN
27	Barraud et al. (84)	2010	France	MV patients	SC/DB	87	59.1 (15.9)	39	NR	9 (4.6)	Probiotics+EN
						80	61.8 (15.5)	44	NR	9.7 (4.8)	Placebo+EN
28	Frohmader et al. (85)	2010	Australia	Critical patients in ICU	SC/DB	20	60.8 (15.6)	65	22.2 (8.9)	NR	Probiotics+EN
						25	65.5 (9.8)	28	23.8 (10.2)	NR	Placebo+EN
29	Morrow et al. (29)	2010	America	MV patients	SC/DB	73	67.5 (31.11)	33	22.7 (7.5)	NR	Probiotics+EN
						73	61.5 (26.67)	46	23.7 (8.0)	NR	Prebiotics+EN
30	Ferrie and Daley (86)	2011	Australia	Critically ill patients with diarrhea	SC/SB	18	56.2 (19.4)	44	27.7 (6.3)	NR	Synbiotics+EN
						18	61.7 (17.5)	44	29.6 (6.1)	NR	Prebiotics+EN
31	Tan et al. (87)	2011	China	ICU patients with severe TBI	SC/DB	26	40.5 (13.0)	73	14.8 (3.6)	6.5 (1.4)	Probiotics+EN
						26	40.8 (12.8)	81	14.3 (3.6)	6.3 (1.4)	EN
32	Hayakawa et al. (88)	2012	Japan	MV patients	SC/OP	31	74 (14)	45	NR	NR	Synbiotics+EN
						16	75 (7)	75	NR	NR	EN
33	Malian et al. (89)	2012	America	Critical patients in SICU	SC/DB	36	60	59	16.7	NR	Probiotics+EN
						33				NR	Placebo+EN

(Continued)

TABLE 1 | Continued

ID	Author	Year	Country	Diseases	Design	*N*	Mean age (SD)	Male (%)	APACHE II Score	SOFA Score	Intervention
34	Plaudis et al. (90)	2012	Latvia	Severe acute pancreatitis patients with organ failure	SC/OP	30	NR	37	8.8 (3.6)	NR	Synbiotics+EN
						28	NR		8.6 (4.9)	NR	Prebiotics+EN
						32	NR		6.8 (4.3)	NR	EN
35	Cui et al. (91)	2013	China	Severe acute pancreatitis patients with organ failure	SC/OP	23	44.9 (19.3)	70	≥8	NR	Probiotics+EN
						25			≥8	NR	EN
						22			≥8	NR	PN
36	Elke et al. (92)	2013	Germany	ICU patients with severe sepsis or septic shock	MC/OP	328	66 (12.7)	62	20 (5.8)	7 (3.6)	EN
						25	61 (10.4)	68	16 (4.4)	6 (2.2)	TPN
37	Tan et al. (93)	2013	China	SICU patients with severe TBI	SC/DB	26	40.5 (13.0)	73	14.8 (3.6)	6.5 (1.4)	Probiotics+EN
						26	40.8 (12.8)	81	14.3 (3.6)	6.3 (1.4)	EN
38	Wang et al. (94)	2013	China	ICU patients with severe acute pancreatitis	SC/DB	62	42.6 (13.8)	52	12.88 (3.19)	NR	Probiotics+EN
						61	43.7 (13.7)	52	13.27 (2.86)	NR	EN
						60	41.7 (11.4)	57	14.63 (3.67)	NR	TPN
39	Lopez de Toro et al. (95)	2014	Spain	ICU patients with multi-organ failure	SC/DB	46	68.5 (19.26)	68.5	20 (8.1)	9 (3.0)	Synbiotics+EN
						43	70 (14.07)		22 (5.9)	9 (3.0)	EN
40	Sanaie et al. (96)	2014	Iran	Critical patients in ICU	SC/DB	20	33.60 (5.50)	65	22.8 (4.73)	12.25 (2.57)	Probiotics+EN
						20	35.60 (5.03)	70	22.45 (4.57)	12.55 (2.6)	EN
41	Zhu et al. (34)	2014	China	Severe acute pancreatitis patients with organ failure	SC/DB	20	43.5 (17.5)	55	≥8	NR	Probiotics+EN
						19	42.0 (16.5)	53	≥8	NR	Placebo+EN
42	Fu et al. (97)	2015	China	Patients with severe acute pancreatitis	SC/OP	36	48.9 (12.2)	NR	11.4 (4.9)	NR	Probiotics+EN
						36	51.3 (13.6)	NR	12.3 (5.1)	NR	TPN
43	Kim et al. (98)	2015	South Korea	ICU patients after living donor liver transplantation	SC/OP	17	52 (7)	88	NR	NR	EN
						19	52 (5.5)	95	NR	NR	TPN
44	Rongrungruang et al. (99)	2015	Thailand	MV patients	SC/OP	75	68.95 (18.45)	60	19.88 (6.89)	NR	Probiotics+EN
						75	73.09 (13.16)	57	19.41 (7.04)	NR	EN
45	Fan et al. (100)	2016	China	NICU patients with severe TBI	SC/OP	80	41.22 (16.77)	51	NR	NR	EN
						40	41.56 (15.10)	53	NR	NR	TPN
46	Malik et al. (101)	2016	Malaysia	Critical patients in ICU	SC/DB	24	60 (14.4)	67	22.12 (6.0)	NR	Probiotics+EN
						25	55 (17.7)	68	23 (8.9)	NR	Placebo+EN
47	Zarinfar et al. (102)	2016	Iran	MV patients	SC/DB	30	NR	NR	NR	NR	Probiotics+EN
						30	NR	NR	NR	NR	Placebo+EN
48	Zeng et al. (32)	2016	China	MV patients	MC/OP	118	50.2 (18.2)	62	14.7 (3.9)	NR	Probiotics+EN
						117	54.6 (17.9)	56	16.6 (4.3)	NR	EN
49	Alberda et al. (103)	2018	Canada	Critical patients in ICU	SC/OP	16	59.9 (15.6)	75	25.5 (5.39)	NR	Probiotics+EN
						16	57.5 (15.0)	63	25.9 (9.70)	NR	EN

(Continued)

TABLE 1 | Continued

ID	Author	Year	Country	Diseases	Design	*N*	Mean age (SD)	Male (%)	APACHE II Score	SOFA Score	Intervention
50	Fazilaty et al. (104)	2018	Iran	ICU patients with multiple trauma	SC/DB	20	NR	90	62 (8)	5 (1.3)	Prebiotics+EN
						20	NR	90	62 (8.5)	9 (3.0)	Placebo + EN
51	Kooshki et al. (105)	2018	Iran	MV patients	SC/DB	30	54.37 (19.18)	40	22.7 (7.5)	NR	Prebiotics+ EN
						30	59.53 (17.37)	63	23.7 (8)	NR	EN
52	Reiginer et al. (106)	2018	French	MV patients	MC/OP	1,202	66 (14)	67	NR	11 (3)	EN
						1,208	66 (14)	67	NR	11 (3)	TPN
53	Shimizu et al. (107)	2018	Japan	Patients MV for ≥72 h and diagnosed sepsis	SC/SB	35	74 (13.33)	71	19 (7.4)	NR	Synbiotics+EN
						37	74 (12.59)	59	20 (8.9)	NR	EN
54	Tuncay et al. (108)	2018	Turkey	Critical patients in NICU	SC/DB	23	73.9 (15.3)	39	NR	NR	Prebiotics+EN
						23	71.8 (20.0)	61	NR	NR	EN
55	Mahmoodpoor et al. (31)	2019	Iran	MV patients	MC/DB	48	59.1 (12.9)	54	24.1 (6.2)	NR	Probiotics+EN
						54	57.5 (14.5)	54	22.8 (4.7)	NR	Placebo+EN

DB, double-blind; EN, enteral nutrition; GCS, Glasgow coma scale; MC, multi-center; MV, mechanical ventilation; NICU, neurological intensive care unit; NR, not reported, OP, open study; RCT, randomized controlled trials; SB, single-blind; SC, single-center; SD, mean difference; SICU, Surgical intensive care unit; TBI, traumatic brain injuries; TPN, total parenteral nutrition.

7,119 patients) from 24 countries all over the world carried out between 1995 and 2019 were included (**Figure 1**). A total of 49 articles were published in English, 5 were in Chinese and 1 was in Spanish. Twenty-four (45%) of 55 trials recruited patients from Europe, 23 (42%) from Asia, 6 (15%) from the America and 2 (3%) from Oceania. Sample sizes varied greatly from 17 to 2410, with a mean of 60 participants (SD = 53). The mean age was 53 years old (SD = 12) for both men and women. Of these participants, 4,358 (61%) of 7,119 of the sample population were male. Eleven (20%) of 55 studies randomly assigned participants to three or more groups. Nine (16%) of 55 studies were multi-center studies, 32 (58%) of 55 studies were double-blind studies and 21 (38%) were open-label studies. Mixed diseases in ICU were the most included diseases, followed by MV support, patients with SAP, severe multiple trauma, victims of brain trauma alone and severe burns. Twenty seven (49%) of 55 studies were of high quality. Nineteen (35%) of 55 studies were of moderate quality (**Figures 2**, **3**). A description of the included studies, interventions, and outcomes is presented in **Tables 1**–**3**. The details of the design, management description and antibiotics are shown in **Supplementary File 2**.

Primary Outcome

The primary analysis was based on the 43 studies comprising 6,215 patients. **Figure 4** displays the network of eligible comparisons for NI. All treatment had at least one EPN-controlled trial. Only synbiotic therapy was not directly compared with probiotic and TPN therapy in the network. **Table 4** shows the results of NMA for NI. In terms of preventing the efficacy of NI, synbiotic (OR 0.37; 95% CrI 0.22–0.61) and probiotic (OR 0.52; 95% CrI 0.34–0.77) therapy were associated with lower morbidity than EPN. By contrast, TPN was worse than EPN (OR 2.29; 95% CrI 1.48–3.67). **Figure 5** shows the SUCRA ranking curve of NI. Synbiotic treatment was the best choice in preventing NI, whereas TPN was the worst.

Secondary Outcomes

The network of eligible comparisons for secondary outcomes is presented in **Supplementary Files 5, 6**. **Figure 6** presents the results of NMA for secondary outcomes. In terms of improving the efficacy of HAP, CRBIS, UTI and sepsis, synbiotic therapy was more effective than EPN, and the results of the network were OR 0.34; 95% CrI 0.11–0.85, OR 0.08; 95% CrI 0.01–0.80, OR 0.27; 95% CrI 0.08–0.71 and OR 0.34; 95% CrI 0.16–0.70, respectively. In terms of shortening the duration of MV, probiotics were more effective than EPN (MD −3.93; 95% CrI −7.98 to −0.02). In terms of preventing the efficacy of diarrhea, prebiotics were more effective than EPN (OR 0.24; 95% CrI 0.05–0.94). By contrast, TPN was worse than EPN on shortening of hospital LOS (MD 4.23; 95% CrI 0.97–7.33). No regimen significantly improved other secondary outcomes. Details of network plot graph, results of the consistent model and forest plot of the effect estimate are shown in **Supplementary File 6**. The SUCRA ranking curve showed that synbiotic therapy was the best choice for HAP, VAP, BSIs, CRBIS, sepsis, hospital mortality, ICU mortality and hospital LOS, while TPN was the worst choice for all secondary outcomes except diarrhea (**Supplementary File 12**).

Direct Meta-Analysis

The forest plot of the pairwise and network effect estimate on NI is shown in **Figure 5**. The detailed results of all outcomes in pairwise meta-analysis are shown in **Supplementary Files 5, 6**.

TABLE 2 | Description of included studies.

	Author	Diseases	*N*	Intervention	Details of intervention	Dose or volume of intervention
1	Braga et al. (62)	SICU patients undergoing curative surgery for gastric or pancreatic cancer	50	EN	Impart+standard formula	25 kcal/kg.day^{-1}
			27	TPN	Isonitrogenous isocaloric	
2	Kudsk et al. (63)	ICU patients with severe trauma	33	EN	Impart, Immun-Aid	Mean 1,400 kcal/day
			19	TPN	NR	NR
3	Bleichner et al. (64)	Critical patients in ICU	64	Probiotics+EN	**Probiotics:** S. boulardii **EN:** Intact protein standard diet without fiber or lactose	500 mg QID
			64	Placebo+EN	**Placebo:** Powder was indistinguishable from the S. boulardii powder **EN:** Intact protein standard diet without fiber or lactose	500 mg QID
4	Falcão De Arruda and De Aguilar-Nascimento (65)	ICU patients with TBI	10	Synbiotics+EN	Fermented milk (Lactobacillus johnsonii)	Fermented milk 240 ml QD
			10	EN	Standard formula	NR
5	Jain et al. (27)	Critical patients in ICU	45	Synbiotics+EN	**Probiotics (Trevis^{TM})**: L. acidophilus La5, L. bulgaricus, Bifidobacterium lactis Bb-12, Streptococcus thermophilus **Prebiotics**: oligofructose EN: NR	Probiotic 4 × 10^9 cfu TID Prebiotic 7.5 g BID
			45	Placebo+EN	**Placebo:** Sucrose powder **EN:** NR	Powdered sucrose capsules TID
6	Lu et al. (66)	Critical patients with severe burns	20	Synbiotics+EN	**Probiotics**: Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei subsp paracasei, Lactobacillus plantarum **Prebiotics**: Betaglucan, Inulin, Pectin, Resistant starch EN: Nutrison Fibre	Probiotic 4 × 10^{10} cfu QD Prebiotic 10 g QD
			20	Prebiotics+EN	**Prebiotics**: Betaglucan, Inulin, Pectin, Resistant starch **EN:** Nutrison Fibre	10 g QD
7	Sun et al. (67)	Critical patients with severe burns	50	EN	Flicare	NR
			50	TPN	Harris-Benedict formula	125–146 kJ/kg
8	Klarin et al. (68)	Critical patients in ICU	8	Probiotics+EN	**Probiotics**: Lactobacillus plantarum 299v	Probiotics: 5 × 10^{10} cfu Q6h 3 days
			7	EN	NR	NR
9	McNaught et al. (28)	Critical patients in ICU	52	Probiotics+EN	**Probiotics**: Proviva (L. plantarum 299 v)	Probiotics:2.5 × 10^9 cfu QD
			51	EN	EN	EN
10	Morrow et al. (69)	MV patients	19	Probiotics+EN	Lactobacillus GG	1 × 10^9 cfu BID
			21	Placebo+EN	Inactive plant starch inulin	BID
11	Kotzampassi et al. (70)	SICU patients with severe multiple trauma	35	Synbiotics+EN	Synbiotic 2000 Forte **Probiotics**: Pediococcus pentoseceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei ssp 19, L. plantarum 2,362 **Prebiotics**: inulin, oat bran, pectin, resistant starch	Probiotic 4 × 10^9 cfu QD Prebiotic 10 g QD
			30	Placebo+EN	**Placebo:** Maltodextrin	QD
12	Petrov et al. (71)	SICU patients with severe multiple trauma	35	EN	Peptamen	Daily 30 kcal/kg and 1.5 g/kg of protein (ideal body weight)
			34	TPN	10% dextrose solution, 10% amino acid solution, and 10% fat emulsion	

(Continued)

TABLE 2 | Continued

	Author	Diseases	*N*	Intervention	Details of intervention	Dose or volume of intervention
13	Spindler-Vesel et al. (72)	SICU patients with severe multiple trauma	26	Synbiotics+EN	Synbiotic 2000 **Probiotics**: Lactobacillus: Pediococcus pentosaceus 5–33:3, Lactococcus raffinolactis 32–77:1, Lactobacillus paracasei subsp paracasei 19, Lactobacillus plantarum 2362 **Prebiotics**: Glucan, inulin, pectin, resistant starch	Probiotic 4 × 10^{10} cfu QD Prebiotic 10 g QD
			29	Prebiotics+EN	Nova Source: fermentable fibers	2.2 g per 100 mL
			58	EN	**Nutricomp peptide Alitraq**: Glutamine, arginine, α-linolenic acid	1.55 g glutamine, 446 mg arginine, 154 mg α-linolenic acid per 100 mL
14	Spindler-Vesel et al. (72)	MV > 2 days critical patients in ICU	40	EN	NR	NR
			40	TPN	Identical amounts of fat, carbohydrate, and protein.	NR
15	Alberda et al. (74)	Critial patients in ICU	10	Probiotics+EN	**VSL#3**: Lactobacillus, Bifidobacterium, Streptococcus salivarius subsp. Thermophilus	Probiotics: 4.5 × 10^{11} cfu BID EN: 25–30 kcal/kg, 1.2–1.5 g/kg protein
			18	EN	**Jevity Plus**	25–30 kcal/kg, 1.2–1.5 g/kg protein
16	Casas et al. (75)	Severe acute pancreatitis patients with organ failure	11	EN	PEPTISORB	1.5–2 g proteins/kg/day and 30–35 kcal/kg/day
			11	TPN	NR	1.5–2 g proteins/kg/day and 30–35 kcal/kg/day
17	Karakan et al. (76)	Severe acute pancreatitis patients with organ failure	15	Prebiotics+EN	**Multifiber:** Soluble fibers and insoluble fibers	24 g per day
			15	EN	**EN:** No prebiotics, no placebo	2,000 kcal/d
18	Olah et al. (77)	Severe acute pancreatitis patients with organ failure	33	Synbiotics+EN	Synbiotic 2000 Forte **Probiotics**: Pediococcus pentoseceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei ssp 19, L. plantarum 2,362 **Prebiotics**: Inulin, oat bran, pectin, resistant starch	Probiotic 4 × 10^{10} cfu QD Prebiotic 10 g QD
			29	Prebiotics+EN	Plant fibers (Betaglucan, inulin, pectin, resistant starch)	10 g QD
19	Sramek et al. (78)	Critical patients in ICU	15	Synbiotics+EN	Synbiotic 2000 Forte **Probiotics**: Pediococcus pentoseceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei ssp 19, L. plantarum 2,362 **Prebiotics**: Inulin, oat bran, pectin, resistant starch, inulin, oat bran, pectin, resistant starch	Probiotic 4 × 10^{10} cfu QD Prebiotic 10 g QD
			11	Prebiotics+EN	Tea	NR
20	Besselink et al. (33)	Patients with predicted severe acute pancreatitis	152	Probiotic+EN	**Probiotic** (Ecologic 641): six different strains of freeze-dried, viable bacteria: Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum, Bifidobacterium lactis) EN: Nutrison Multi Fibre	Probiotic 10^{10} cfu totally daily
			144	EN	Nutrison Multi Fibre	NR
21	Forestier et al. (79)	Critical patients in ICU	102	Probiotics+EN	**Probiotics**: Lactobacillus casei rhamnosus	10^{9} cfu BID
			106	Placebo+EN	**Placebo:** Growth medium without bacteria	NR

(Continued)

TABLE 2 | Continued

	Author	Diseases	*N*	Intervention	Details of intervention	Dose or volume of intervention
22	Klarin et al. (80)	Critical patients in ICU	22	Synbiotics+EN	**Probiotics**: 299 Lactobacillus plantarum 8×10^8 cfu /ml **Prebiotics**: Oatmeal	Probiotics: given as 6 × 100 ml doses every 12 h and after 50 ml given BID
			22	Prebiotics+EN	**Prebiotics**: Oatmeal	Same oatmeal gruel mixed with lactic acid
23	Doley et al. (81)	Severe acute pancreatitis patients with organ failure	25	EN	NR	2,500–2,700 kcal/day, 120–130 g/day of protein
			25	TPN	NR	2,500–2,700 kcal/day, 120–130 g/day of protein
24	Giamarellos-Bourboulis et al. (82)	SICU patients with severe multiple injuries	36	Synbiotics+EN	Synbiotic 2000 Forte **Probiotics**: Pediococcus pentoseceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei ssp 19, L. plantarum 2,362 **Prebiotics**: Inulin, oat bran, pectin, resistant starch **EN**: Intestamin	Probiotic: 4×10^{10} cfu QD Prebiotic:10 g QD
			36	EN	Intestamin	NR
25	Knight et al. (26)	MV patients	130	Synbiotics+EN	Synbiotic 2000 Forte **Probiotics**: Pediococcus pentoseceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei ssp 19, L. plantarum 2,362 **Prebiotics**: Inulin, oat bran, pectin, resistant starch **EN**: Nutrison Energy	Probiotic 4×10^{10} cfu BID Prebiotic 10 g BID
			129	Placebo+EN	**Placebo:** Crystalline cellulose **EN:** Nutrison Energy	10 g BID
26	Moses et al. (83)	ICU patients with acute organophosphate poisoning needing invasive mechanical ventilatory support	29	EN	Hypocaloric EN	Maximum of 1,000 cal/d and protein 28.32 g
			30	TPN	Glucose and electrolyte	Maximum of 1,000 cal/d and protein 28.32 g
27	Barraud et al. (84)	MV patients	87	Probiotics+EN	**Probiotics:** Ergyphilus Lactobacillus rhamnosus GG, Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium bifidum **EN:** Fresubin	Probiotics: 2×10^{10} cfu QD EN: 30–35 kcal/kg
			80	Placebo+EN	**Placebo:** Excipient **EN:** Fresubin	Placebo: NR EN: 30–35 kcal/kg
28	Frohmader et al. (85)	Critical patients in ICU	20	Probiotics+EN	**Probiotics (VSL#3):** Lactobacillus, Bifidobacterium, Streptococcus salivarius subsp. Thermophilus **EN:** Isosource or Renal or Diabetic Resource (Novartis, Melbourne, Australia)	Probiotics: 4.5×10^{11} cfu BID EN: 25 to 35 cal/kg per day and 0.8 to 1.5 g protein per kilogram per day
			25	Placebo+EN	**Placebo:** Free of fiber and prebiotic additives **EN:** Isosource or Renal or Diabetic Resource (Novartis, Melbourne, Australia)	Placebo: BID EN: 25 to 35 cal/kg per day and 0.8 to 1.5 g protein per
29	Morrow et al. (29)	MV patients	73	Probiotics+EN	**Probiotics**: Lactobacillus rhamnosus GG EN: NR	Probiotics: 2×10^9 cfu BID
			73	Prebiotics+EN	**Prebiotics**: Inulin **EN**: NR	BID
30	Ferrie and Daley (86)	Critically ill patients with diarrhea	18	Synbiotics+EN	**Probiotics**: Lactobacillus rhamnosus GG **Prebiotics**: inulin powder **EN:** standard feeding formula, which is a 1-calorie per mL oat fiber–containing formula	Probiotic: 10^{10} cfu QD Prebiotic:280 mg QD

(Continued)

TABLE 2 | Continued

	Author	Diseases	*N*	Intervention	Details of intervention	Dose or volume of intervention
			18	Prebiotics+EN	**Prebiotics**: Inulin powder **EN:** standard feeding formula, which is a 1-calorie per mL oat fiber–containing formula	Prebiotic:280 mg QD
31	Tan et al. (87)	ICU patients with severe TBI	26	Probiotics+EN	**Probiotics:** Golden Bifid: 0.5×10^8 cfu Bifidobacterium longum, 0.5×10^7 cfu Lactobacillus bulgaricus,0.5×10^7 cfu Streptococcus thermophilus **EN:** (3.8 g protein, 13.8 g carbohydrate, 3.4 g fat/100 ml, osmolarity 250 mOsm/l, no fibers)	Probiotics:10^9 cfu per day EN: 30 kcal/kg body weight/day
			26	EN	**EN:** (3.8 g protein, 13.8 g carbohydrate, 3.4 g fat/100 ml, osmolarity 250 mOsm/l, no fibers)	30 kcal/kg body weight/day
32	Hayakawa et al. (88)	MV Patients	31	Synbiotics+EN	**Probiotics** (Yakult): 1×10^8 cfu /g Bifidobacterium breve strain Yakult, 1×10^8 cfu /g Lactobacillus casei strain Shirota **Prebiotics**: galactooligosaccharides **EN:** Medief (100 kcal, protein 4.5 g, fat 2.8 g, carbohydrate 14.2 g, dietary fiber 1.2 g in 100 ml) (Ajinomoto)	Probiotics: 1 g TID Prebiotics: 5 g TID EN: According to the patient's requirements
			16	EN	Medief (100 kcal, protein 4.5 g, fat 2.8 g, carbohydrate 14.2 g, dietary fiber 1.2 g in 100 ml) (Ajinomoto)	According to the patient's requirements
33	Malian et al. (89)	Critical patients in SICU	36	Probiotics+EN	**Probiotics:** Lactobacillus GG **EN:** NR	NR
			33	Placebo+EN	**Placebo:** NR **EN:** NR	NR
34	Plaudis et al. (90)	Severe acute pancreatitis patients with organ failure	30	Synbiotics+EN	Synbiotic 2000 Forte **Probiotics**: Pediococcus pentoseceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei ssp 19, L. plantarum 2,362 **Prebiotics**: inulin, oat bran, pectin, resistant starch EN: Nutrison, standard whole protein feeding formula	Probiotic 4×10^9 cfu BID Prebiotic 10 g BID EN 2,500 kcal/day
			28	Prebiotics+EN	**Prebiotics**: Inulin, oat bran, pectin, resistant starch EN: Nutrison, standard whole protein feeding formula	Prebiotic 10 g BID EN 2,500 kcal/day
			32	EN	Nutrison, standard whole protein feeding formula	2,500 kcal/day
35	Cui et al. (91)	Severe acute pancreatitis patients with organ failure	23	Probiotics+EN	**Protiotics:** Bifidobacterium **EN:** Peptisorb, Nutrison Fibre	**Protiotics:**10.416×10^9 cfu Q12h, **EN: NR**
			25	EN	**EN:** Peptisorb, Nutrison Fibre	**EN:** NR
			22	PN	Glucose, electrolyte, fat emulsion, amino acid	**EN:** NR
36	Elke et al. (92)	ICU patients with severe sepsis or septic shock	328	EN	NR	NR
			25	TPN	NR	NR
37	Tan et al. (93)	SICU patients with severe TBI	26	Probiotics+EN	**Protiotics:** Golden Bifid: 0.5×10^8 cfu Bifidobacterium longum, 0.5×10^7 cfu Lactobacillus bulgaricus,0.5×10^7 cfu Streptococcus thermophilus **EN:** Standard formula	**Protiotics:**10^9 cfu per day **EN:** NR
			26	EN	Standard formula	NR
38	Wang et al. (94)	ICU patients with severe acute pancreatitis	62	Probiotics+EN	**Protiotics:** Bacillus subtilis 1.8×10^9 cfu /g, Enterococcus faecium 2.0×10^8 cfu /g **EN:** PEPTISORB	**Protiotics:** 0.5 g TID **EN:** 2 g proteins/kg/d and 35 kcal/kg/d
			61	EN	**EN:** PEPTISORB	**EN:**2 g proteins/kg/d and 35 kcal/kg/d

(Continued)

TABLE 2 | Continued

	Author	Diseases	*N*	Intervention	Details of intervention	Dose or volume of intervention
			60	TPN	TPN	2 g proteins/kg/d and 35 kcal/kg/d, A ratio of 120:1 of non-protein calories-to-nitrogen
39	Lopez de Toro et al. (95)	ICU patients with multi-organ failure	46	Synbiotics+EN	**Probiotics (**Drink Simbiotic): streptococcus Thermophilus, lactobacillus bulgaricus, Lactobacilluscasei, lactobacillus acidophilus, bifidobacterium, Escherichia coli, coliformes **Prebiotics**: NR	Max 4.8 × 10^9 cfu /ml
			43	EN	NR	NR
40	Sanaie et al. (96)	Critical patients in ICU	20	Probiotics+EN	**Probiotics** (VSL#3): Lactobacillus acidophilus, Bifidobacterium longus, Bifidobacterium bifidum &Bifidobacterium infantalis **EN:** Fresubin original fibre	Probiotics:9.0 × 10^9 cfu BID EN: Energy requirements 25–30 kcal/kg and protein 1.2–1.5 g/kg.
			20	EN	**EN:** Fresubin original fibre	Energy requirements 25–30 kcal/kg and protein 1.2–1.5 g/kg.
41	Zhu et al. (34)	Severe acute pancreatitis patients with organ failure	20	Probiotics+EN	**Probiotics:** Clostridium Butyricum (miyarisan) **EN:** NR	0.7 × 10^6 cfu BID
			19	Placebo+EN	**Placebo:** Starch **EN:** NR	The same capsule type and amount
42	Fu et al. (97)	Patients with severe acute pancreatitis	36	Probiotics+EN	**Probiotics:** live combined bacillus subtilis and enterococcusfaecium **EN:** Peptisorb, Nutrison Fibre	NR
			36	TPN	NR	1.0–1.5 g proteins/kg/day and 25–30 kcal/kg/day
43	Kim et al. (98)	ICU patients after living donor liver transplantation	17	EN	Mediwell RTH 500	NR
			19	TPN	NR	NR
44	Rongrungruang et al. (99)	MV patients	75	Probiotics+EN	**Probiotics:** Lactobacillus casei (Yakult) (Shirota strain) **EN:** NR	8 × 10^9 cfu for oral care after standard oral care QD. 8 × 10^9 cfu enteral feeding QD
			75	EN	NR	NR
45	Fan et al. (100)	NICU patients with severe TBI	80	EN	Nutrison Fibre	105–126 KJ/d
			40	TPN	2:1 for carbohydrates to lipids and 100:1 for calorie nitrogen ratio	105–126 KJ/d
46	Malik et al. (101)	Critical patients in ICU	24	Probiotics+EN	**Probiotics:** Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis **EN:** Osmolite 1 cal (standard formula), Glucerna (glucose intolerance formula), Peptamen (semielemental formula), and Novasource Renal (electrolyte and fluid restriction).	**Probiotics:**3 × 10^9 cfu BID **EN:**25 kcal kg^{-1} d^{-1}
			25	Placebo+EN	**Placebo:** Similar appearance and taste, **EN:** Osmolite 1 cal (standard formula), Glucerna (glucose intolerance formula), Peptamen (semielemental formula), and Novasource Renal (electrolyte and fluid restriction).	**Placebo:** 3 g BID **EN:**25 kcal kg^{-1} d^{-1}
47	Zarinfar et al. (102)	MV patients	30	Probiotics+EN	**Probiotics:** Lactobacillus GG	TID
			30	Placebo+EN	**Placebo:** NR	TID

(Continued)

TABLE 2 | Continued

	Author	Diseases	*N*	Intervention	Details of intervention	Dose or volume of intervention
48	Zeng et al. (32)	MV patients	118	Probiotics+EN	**Probiotics:** Medilac-S: Bacillus subtilis 4.5×10^9 cfu /0.25 g and Enterococcus faecalis 0.5×10^9 cfu /0.25 g **EN:** NR	**Probiotics:**0.5 g TID EN: NR
			117	EN	NR	NR
49	Alberda et al. (103)	Critical patients in ICU	16	Probiotics+EN	**Probiotics:** Lactobacillus casei (Danactive)	1×10^{10} cfu BID
			16	EN	No prebiotics, no placebo	NR
50	Fazilaty et al. (104)	ICU patients with multiple trauma	20	Prebiotics+EN	**Prebiotics:** b-glucan **EN:** high-protein enteral diet (20% protein, 30% lipid, and 50% carbohydrate)	3 g QD 25–30 kcal/kg
			20	Placebo + EN	**Placebo:** Maltodextrin **EN:** high-protein enteral diet (20% protein, 30% lipid, and 50% carbohydrate)	3 g QD 25–30 kcal/kg
51	Kooshki et al. (105)	MV patients	30	Prebiotics+ EN	**Prebiotics:** Fenugreek seed powder **EN:** NR	3 g BID
			30	EN	NR	NR
52	Reiginer et al. (106)	MV patients	1,202	EN	Isosmotic, isocaloric, normal-protein, polymeric preparations	Daily calorie target in kcal/kg of actual bodyweight was 20–25 during the first 7 days then 25–30 from day 8 to extubation.
			1,208	TPN	Three groups of macronutrients	Daily calorie target in kcal/kg of actual bodyweight was 20–25 during the first 7 days then 25–30 from day 8 to extubation
53	Shimizu et al. (107)	Patients MV for ≥72 h and diagnosed sepsis	35	Synbiotics+EN	**Probiotics** (Yakult BL Seichoyaku): 1×10^8 cfu /g B. breve strain /g and 1×10^8 cfu /g L. casei strain Shirota **Prebiotics**: galactooligosaccharides (Oligomate S-HP) **EN:** Standard polymeric diet Glucerna®-Ex 1 kcal/mL; 51:17:32 ratio of carbohydrate, protein, and fat; 370 mOsm/L; fiber 1.4 g/100 mL	Probiotics: 3 g QD Prebiotics: 10 g QD EN: 25–30 kcal/kg ideal body weight per day as the calorie goal
			37	EN	Standard polymeric diet Glucerna®-Ex 1 kcal/mL; 51:17:32 ratio of carbohydrate, protein, and fat; 370 mOsm/L; fiber 1.4 g/100 mL	25–30 kcal/kg ideal body weight per day as the calorie goal
54	Tuncay et al. (108)	Critical patients in NICU	23	Prebiotics+EN	**Prebiotics:** Fructo-oligosaccharides (Jevity, 1 kcal/1 ml) **EN:** Standard formula (Osmolite, 1 kcal/1 ml)	Prebiotics:5.3 g QD 1 g/kg/ day EN:30–40 ml/kg/day
			23	EN	Standard formula (Osmolite, 1 kcal/1 ml)	1 g/kg/ day and 30–40 ml/kg/day
55	Mahmoodpoor et al. (31)	MV patients	48	Probiotics+EN	**Probiotics:** Lactocare: Lactobacillus species (casei, acidophilus, rhamnosus, bulgaricus), Bifidobacterium species (breve, longum), Streptococcus thermophilus. **EN:** Standard formula (1 kcal/mL; Ensure)	Probiotics:10^{10} cf u BID EN:25 kcal/kg
			54	Placebo+EN	**Placebo:** Sterile maize starch powder **EN:** Standard formula (1 kcal/mL;Ensure)	Placebo: BID EN:25 kcal/kg

CFU, colony forming units; EN, enteral nutrition; GCS, Glasgow coma scale; MV, mechanical ventilation; NG, nasogastric; NJ, nasojejunal; NR, not reported; OG, orogastric; PN, parenteral nutrition; TBI, traumatic brain injuries; TPN, total parenteral nutrition.

TABLE 3 | Reported clinical outcomes of included studies.

	Intervention	Nosocomial Infection (n/N)							Diarrhea	Mortality (n/N)		Mean LOS (SD)		
		Total	HAP	VAP	BI	CRBIS	UTI	Sepsis		Hospital	ICU	Hospital	ICU	MV
1	EN	6/50	NR	NR	NR	NR	NR	NR	NR	NR	NR	14.3 (5.0)	NR	NR
	TPN	4/27	NR	NR	NR	NR	NR	NR	NR	NR	NR	19.3 (7.3)	NR	NR
2	EN	16/33	2/33	NR	5/33	NR	8/33	NR	NR	2/33	NR	25.7 (8.8)	7.7 (2.8)	3.9 (2.3)
	TPN	13/19	4/19	NR	8/19	NR	4/19	NR	NR	0/19	NR	34.9 (6.0)	15.7 (4.9)	9.0 (4.2)
3	Probiotics+EN	NR	NR	NR	NR	NR	NR	NR	18/64	NR	NR	NR	NR	NR
	Placebo+EN	NR	NR	NR	NR	NR	NR	NR	24/64	NR	NR	NR	NR	NR
4	Synbiotics+EN	5/10	NR	NR	NR	NR	NR	0/10	NR	NR	NR	NR	11.11 (10)	7 (10.37)
	EN	10/10	NR	NR	NR	NR	NR	3/10	NR	NR	NR	NR	22 (37.04)	14 (37.04)
5	Synbiotics+EN	33/45	NR	NR	NR	NR	NR	26/45	NR	22/45	NR	14 (14.81)	7 (9.63)	NR
	Placebo+EN	26/45	NR	NR	NR	NR	NR	33/45	NR	20/45	NR	15 (12.59)	5 (8.148)	NR
6	Synbiotics+EN	8/20	NR	NR	3/20	4/20	NR	NR	NR	2/20	NR	NR	NR	NR
	Prebiotics+EN	11/20	NR	NR	5/20	7/20	NR	NR	NR	1/20	NR	NR	NR	NR
7	EN	NR	NR	NR	NR	NR	NR	NR	18/50	7/50	NR	24.5	NR	NR
	TPN	NR	NR	NR	NR	NR	NR	NR	3/50	10/50	NR	30.2	NR	NR
8	Probiotics+EN	6/8	5/8	NR	0/8	3/8	2/8	NR	NR	2/8	1/8	NR	12 (24.44)	NR
	EN	5/7	2/7	NR	3/7	3/7	1/7	NR	NR	2/7	2/7	NR	11 (33.33)	NR
9	Probiotics+EN	21/52	NR	NR	NR	NR	NR	NR	NR	18/52	NR	NR	5 (5.158)	NR
	EN	22/51	NR	NR	NR	NR	NR	NR	NR	18/51	NR	NR	4 (3.704)	NR
10	Probiotics+EN	2/19	NR	5/19	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo+EN	7/21	NR	10/21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
11	Synbiotics+EN	17/35	19/35	NR	NR	13/35	6/35	6/35	5/35	5/35	5/35	NR	27.7 (15.2)	16.7 (9.5)
	Placebo+EN	23/30	24/30	NR	NR	20/30	13/30	12/30	10/30	9/30	9/30	NR	41.3 (20.5)	29.7 (16.15)
12	EN	7/35	2/35	NR	NR	0/35	2/35	NR	6/35	2/35	NR	NR	NR	NR
	TPN	25/34	2/34	NR	NR	5/34	4/34	NR	1/34	12/34	NR	NR	NR	NR
13	Synbiotics+EN	5/26	4/26	NR	0/26	0/26	0/26	NR	NR	2/26	2/26	NR	12 (9.481)	11 (8.37)
	Prebiotics+EN	17/29	12/29	NR	2/29	0/29	0/29	NR	NR	2/29	2/29	NR	16 (8.148)	12 (5.185)
	EN	29/58	22/58	NR	2/58	2/58	1/58	NR	NR	3/58	3/58	NR	12.9 (10.6)	9.1 (7.7)
14	EN	14/40	NR	NR	NR	NR	NR	NR	NR	7/40	NR	10.82	7.6	6.25
	TPN	20/40	NR	NR	NR	NR	NR	NR	NR	11/40	NR	12.95	10.32	8.65
15	Probiotics+EN	0/10	NR	NR	NR	NR	NR	0/10	1/10	NR	1/10	NR	NR	NR
	EN	0/18	NR	NR	NR	NR	NR	0/18	3/18	NR	2/18	NR	NR	NR
16	EN	1/11	NR	NR	0/11	0/11	1/11	2/11	NR	0/11	NR	30.2	NR	NR
	TPN	5/11	NR	NR	3/11	2/11	0/11	2/11	NR	2/11	NR	30.7	NR	NR
17	Prebiotics+EN	3/15	NR	NR	NR	NR	NR	1/15	NR	2/15	NR	10 (4.44)	6 (2.22)	NR
	EN	3/15	NR	NR	NR	NR	NR	2/15	NR	4/15	NR	15 (14.07)	6 (1.481)	NR
18	Synbiotics+EN	9/33	2/33	NR	NR	NR	3/33	3/33	NR	2/33	NR	14.9	NR	NR
	Prebiotics+EN	15/33	4/29	NR	NR	NR	3/29	5/29	NR	6/29	NR	19.7	NR	NR
19	Synbiotics+EN	9/15	NR	NR	NR	NR	NR	NR	NR	0/15	NR	NR	14 (16.3)	NR
	Prebiotics+EN	4/10	NR	NR	NR	NR	NR	NR	NR	1/11	NR	NR	10 (9.63)	NR
20	Probiotic+EN	46/152	24/152	NR	32/152	NR	1/152	1/152	25/152	24/152	NR	28.9 (41.5)	6.6 (17.1)	NR
	EN	41/144	16/144	NR	22/144	NR	2/144	2/144	28/144	9/144	NR	23.5 (25.9)	3 (9.3)	NR
21	Probiotics+EN	24/102	NR	24/102	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo+EN	24/106	NR	24/106	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
22	Synbiotics+EN	11/22	7/22	NR	2/22	1/22	2/22	NR	NR	3/22	2/22	NR	5.5 (14.44)	4.4 (12.07)
	Prebiotics+EN	16/22	9/22	NR	3/22	3/22	1/22	NR	NR	2/22	2/22	NR	8.8 (48.81)	7.3 (14.52)
23	EN	16/25	NR	NR	5/25	NR	NR	4/25	NR	5/25	NR	42 (23.3)	10 (11)	NR
	TPN	15/25	NR	NR	8/25	NR	NR	3/25	NR	4/25	NR	36 (14.3)	15 (15)	NR
24	Synbiotics+EN	NR	NR	15/36	5/36	NR	6/36	5/36	NR	5/36	NR	NR	NR	NR
	EN	NR	NR	16/36	13/36	NR	11/36	13/36	NR	10/36	NR	NR	NR	NR
25	Synbiotics+EN	12/130	NR	12/130	NR	NR	NR	NR	7/130	35/130	28/130	19 (20.74)	6 (5.926)	5 (5.185)

(Continued)

TABLE 3 | Continued

	Intervention	Nosocomial Infection (n/N)							Diarrhea	Mortality (n/N)		Mean LOS (SD)		
		Total	HAP	VAP	BI	CRBIS	UTI	Sepsis		Hospital	ICU	Hospital	ICU	MV
	Placebo+EN	17/129	NR	17/129	NR	NR	NR	NR	9/129	42/129	34/129	18 (18.52)	7 (8.148)	5 (5.926)
26	EN	17/29	NR	12/29	NR	3/29	2/29	NR	0/29	3/29	NR	15 (7.8)	10.5 (5.2)	12 (6.3)
	TPN	19/30	NR	10/30	NR	4/30	5/30	NR	1/30	3/30	NR	12 (5.6)	8 (5.6)	10 (5.9)
27	Probiotics+EN	30/87	NR	23/87	NR	3/87	4/87	NR	48/87	27/87	21/87	26.6 (22.3)	18.7 (12.4)	NR
	Placebo+EN	30/80	NR	15/80	NR	11/80	4/80	NR	42/80	24/80	21/80	28.9 (26.4)	20.2 (20.8)	NR
28	Probiotics+EN	NR	NR	NR	NR	NR	NR	NR	NR	5/20	NR	NR	7.3 (5.7)	6 (5.2)
	Placebo+EN	NR	NR	NR	NR	NR	NR	NR	NR	3/25	NR	NR	8.1 (4)	6.71 (5.25)
29	Probiotics+EN	13/73	NR	13/73	NR	NR	NR	NR	46/73	12/73	NR	21.7 (17.4)	14.8 (11.8)	9.6 (7.2)
	Prebiotics+EN	28/73	NR	28/73	NR	NR	NR	NR	57/73	15/73	NR	21.4 (14.9)	14.6 (11.6)	9.5 (6.3)
30	Synbiotics+EN	NR	NR	NR	NR	NR	NR	NR	NR	2/18	NR	54.5 (31.26)	32.04 (24.46)	NR
	Prebiotics+EN	NR	NR	NR	NR	NR	NR	NR	NR	2/18	NR	59.04 (33.92)	29.75 (18.81)	NR
31	Probiotics+EN	9/26	2/10	7/16	0/26	NR	0/26	0/26	NR	3/26	NR	NR	6.8 (3.8)	NR
	EN	15/26	1/7	13/19	1/26	NR	2/26	0/26	NR	5/26	NR	NR	10.7 (7.3)	NR
32	Synbiotics+EN	5/31	5/31	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	EN	3/16	3/16	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
33	Probiotics+EN	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	18	9
	Placebo+EN	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	21	17
34	Synbiotics+EN	2/30	NR	NR	2/30	NR	NR	2/30	NR	0/30	NR	NR	NR	NR
	Prebiotics+EN	2/28	NR	NR	2/28	NR	NR	2/28	NR	1/28	NR	NR	NR	NR
	EN	12/32	NR	NR	7/32	NR	NR	1/32	NR	5/32	NR	NR	NR	NR
35	Probiotics	2/23	NR	NR	NR	NR	NR	NR	NR	1/23	NR	10.4 (3.9)	NR	NR
	EN	5/25	NR	NR	NR	NR	NR	NR	NR	1/25	NR	13.4 (5.2)	NR	NR
	TPN	12/22	NR	NR	NR	NR	NR	NR	NR	3/22	NR	25.8 (6.4)	NR	NR
36	EN	193/328	NR	NR	NR	NR	NR	NR	NR	70/328	NR	NR	29 (27.2)	NR
	TPN	17/25	NR	NR	NR	NR	NR	NR	NR	4/25	NR	NR	12 (25.9)	NR
37	Probiotics+EN	NR	NR	NR	NR	NR	NR	NR	NR	3/26	NR	NR	6.8 (3.8)	NR
	EN	NR	NR	NR	NR	NR	NR	NR	NR	5/26	NR	NR	10.7 (7.3)	NR
38	Probiotics+EN	8/62	NR	NR	NR	NR	NR	8/62	NR	5/62	NR	NR	NR	NR
	EN	13/61	NR	NR	NR	NR	NR	13/61	NR	6/61	NR	NR	NR	NR
	TPN	24/60	NR	NR	NR	NR	NR	24/60	NR	7/60	NR	NR	NR	NR
39	Synbiotics+EN	9/46	NR	NR	NR	NR	NR	NR	NR	19/46	15/46	18.5 (19.26)	9 (4)	10 (3.75)
	EN	13/43	NR	NR	NR	NR	NR	NR	NR	18/43	14/43	24.5 (20.74)	8 (3.5)	8.5 (3.625)
40	Probiotics+EN	2/20	NR	NR	NR	NR	NR	2/20	NR	NR	NR	NR	NR	NR
	EN	5/20	NR	NR	NR	NR	NR	5/20	NR	NR	NR	NR	NR	NR
41	Probiotics+EN	NR	5/20	NR	11/20	NR	2/20	NR	NR	NR	NR	NR	1.21	NR
	Placebo+EN	NR	6/19	NR	13/19	NR	1/19	NR	NR	NR	NR	NR	1.01	NR
42	Probiotics+EN	2/36	NR	NR	NR	NR	NR	NR	NR	1/36	NR	15.4 (8.5)	NR	NR
	TPN	15/36	NR	NR	NR	NR	NR	NR	NR	2/36	NR	23.2 (9.7)	NR	NR
43	EN	1/17	NR	2/17	NR	0/17	NR	NR	NR	0/17	NR	23 (25.3)	6 (4)	NR
	TPN	5/19	NR	5/19	NR	2/19	NR	NR	NR	0/19	NR	24 (16)	6 (1.3)	NR
44	Probiotics+EN	18/75	NR	18/75	NR	NR	NR	NR	19/75	18/75	NR	20 (26)	30.5 (23.5)	NR
	EN	22/75	NR	22/75	NR	NR	NR	NR	14/75	17/75	NR	19 (42)	19 (6.25)	NR
45	EN	NR	13/80	NR	NR	NR	NR	13/80	32/80	16/80	NR	NR	29.52 (7.01)	10.48 (5.80)
	TPN	NR	19/40	NR	NR	NR	NR	19/40	6/40	17/40	NR	NR	36.33 (8.61)	18.63 (5.39)
46	Probiotics+EN	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10.9 (3.9)	8.4 (3.5)
	Placebo+EN	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	15.8 (7.8)	14 (8)
47	Probiotics+EN	7/30	NR	7/30	NR	NR	NR	NR	1/30	5/30	NR	24.1 (5.6)	14.2 (4.7)	NR
	Placebo+EN	15/30	NR	15/30	NR	NR	NR	NR	6/30	16/30	NR	27.4 (6.6)	17.6 (6.5)	NR
48	Probiotics+EN	NR	NR	48/118	NR	NR	NR	NR	NR	26/118	15/118	13.5 (12.4)	18 (13.33)	12 (9.63)
	EN	NR	NR	62/117	NR	NR	NR	NR	NR	25/117	9/117	10.6 (10.2)	22 (33.33)	17 (11.11)

(Continued)

TABLE 3 | Continued

	Intervention	Nosocomial Infection (n/N)							Diarrhea	Mortality (n/N)		Mean LOS (SD)		
		Total	HAP	VAP	BI	CRBIS	UTI	Sepsis		Hospital	ICU	Hospital	ICU	MV
49	Probiotics+EN	1/16	NR	NR	NR	NR	NR	NR	11/16	2/16	1/16	79.56 (116.8)	11.38 (7.4)	NR
	EN	2/16	NR	NR	NR	NR	NR	NR	10/16	2/16	2/16	39.38 (54.74)	15.31 (12.96)	NR
50	Prebiotics+EN	5/20	NR	4/20	NR	0/20	0/20	0/20	NR	1/20	NR	NR	27.55 (7.8)	15 (9.3)
	Placebo + EN	11/20	NR	4/20	NR	3/20	4/20	2/20	NR	4/20	NR	NR	31.2 (15.8)	28 (21.3)
51	Prebiotics+ EN	7/30	NR	7/30	NR	NR	NR	NR	1/30	2/30	NR	24.1 (5.6)	14.2 (4.8)	16.06 (4.81)
	EN	15/30	NR	15/30	NR	NR	NR	NR	10/30	6/30	NR	27.4 (6.6)	17.6 (6.7)	20.26 (6.05)
52	EN	173/ 1,202	NR	113/ 1,202	38/ 1,202	29/ 1,202	18/ 1,202	NR	432/ 1,202	498/ 1,202	429/ 1,202	NR	9 (8.1)	NR
	TPN	194/ 1,208	NR	118/ 1,208	55/ 1,208	27/ 1,208	16/ 1,208	NR	393/ 1,208	479/ 1,208	405/ 1,208	NR	10 (8.9)	NR
53	Synbiotics+EN	10/35	NR	5/35	5/35	NR	NR	NR	NR	3/35	NR	NR	28 (20.74)	NR
	EN	25/37	NR	18/37	5/37	NR	NR	NR	NR	4/37	NR	NR	23 (22.22)	NR
54	Prebiotics+EN	NR	NR	NR	NR	NR	NR	NR	2/23	NR	NR	NR	NR	NR
	EN	NR	NR	NR	NR	NR	NR	NR	12/23	NR	NR	NR	NR	NR
55	Probiotics+EN	NR	NR	NR	NR	NR	NR	NR	7/48	NR	5/48	14.2 (8.6)	11.6 (8)	8.75 (4.79)
	Placebo+EN	NR	NR	NR	NR	NR	NR	NR	15/54	NR	6/54	21.1 (5.7)	18.6 (6.3)	12.08 (7.125)

BI, Bloodstream infection; CRBIS, Catheter-related bloodstream infection; EN, enteral nutrition; HAP, hospital acquired pneumonia; LOS, length of stay; MV, Mechanical ventilation; NR, not reported; SD, standard deviation; TPN, Total parenteral nutrition; UTI, Urinary tract infection; VAP, Ventilator-associated Pneumonia.

Network Heterogeneity, Inconsistency, and Transitivity

The analysis of heterogeneity (**Supplementary File 7**) revealed moderate-to-high global heterogeneity in NI ($I^2 = 62.02\%$), VAP ($I^2 = 54.33\%$), CRBIS ($I^2 = 79.14\%$), diarrhea ($I^2 = 91.11\%$), hospital LOS ($I^2 = 98.56\%$), ICU LOS ($I^2 = 79.47\%$) and duration of MV ($I^2 = 86.10\%$).

In the analysis of inconsistency (**Supplementary File 8**), there was no global inconsistency in all outcomes except diarrhea ($p = 0.0018$). Inconsistencies were found between direct and indirect comparisons of probiotic therapy and EPN for NI ($p = 0.04143$), synbiotic and prebiotic therapy for CRBIS ($p = 0.03569$), synbiotic therapy and EPN for CRBIS ($p = 0.04404$), prebiotic therapy and EPN for CRBIS ($p = 0.02783$), synbiotic and prebiotic therapy for UTI ($p = 0.04033$), synbiotic therapy and EPN for UTI ($p = 0.03591$), prebiotic therapy and EPN for UTI ($p = 0.04071$), probiotic and prebiotic therapy for diarrhea ($p = 0.01030$), probiotic therapy and EPN for diarrhea ($p = 0.01008$), prebiotic therapy and EPN for diarrhea ($p = 0.01060$), and probiotic therapy and TPN for hospital LOS ($p = 0.04520$).

In the assessment of transitivity (**Supplementary File 9**), most of the comparisons had similar mean age, but there were a few comparisons with relatively low or high age. Meta-regressions of mean age did not show that they affected the network estimates, although results from such analyses might suffer from ecological bias.

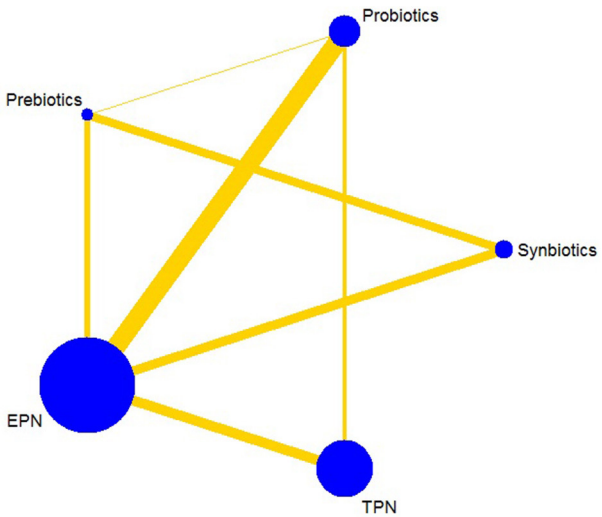

FIGURE 4 | Network plot of all intervention comparisons for nosocomial infection. The size of the nodes corresponds to the total number of participants that study the treatments. The (directly) comparable treatments are linked with a line. The thickness of the line corresponds to the standard error of trials that study this comparison. The colors of the line correspond to the quality of trials that study this comparison. Low risk of bias [green], moderate risk of bias [yellow]. EPN, Enteral nutrition or adjuvant peripheral parenteral nutrition; TPN, Total parenteral nutrition.

Subgroup and Sensitivity Analyses for Primary Outcome

Subgroup analysis of the diseases (**Table 5**) revealed a significant effect on the therapeutic effect of synbiotic therapy except MV patients and patients with initial time of nutrition therapy beyond 48 h, while TPN was shown to increase the morbidity of NI in different disease subgroups except MV patients (OR 1.31 95%

TABLE 4 | Results from pairwise meta-analyses and network meta-analyses on nosocomial infection.

Synbiotics	–	1.90 (0.94, 3.90)	**2.50 (1.50, 4.60)**	–
0.71 (0.38, 1.34)	**Probiotics**	2.90 (0.79, 11.11)	**1.60 (1.10, 2.40)**	**8.30 (2.90, 25.21)**
0.57 (0.32, 1.01)	0.84 (0.44, 1.60)	**Prebiotics**	2.10 (1.00, 4.70)	–
0.37 (0.22, 0.61)	**0.52 (0.34, 0.77)**	0.65 (0.35, 1.15)	**EPN**	**2.00 (1.30, 3.30)**
0.16 (0.08, 0.31)	**0.23 (0.12, 0.39)**	**0.28 (0.13, 0.58)**	**0.44 (0.27, 0.68)**	**TPN**

Data are the ORs (95% CrI) in the column-defining treatment compared with the row-defining treatment. With treatment as the boundary, the lower left part of the table is the result of network meta-analyses, and the upper right part of the table is the result of pairwise meta-analyses. For network meta-analyses, ORs lower than 1 favor the column-defining treatment (e.g., column 1 vs. row 4 in the lower left part of the table (synbiotics vs. EPN) is the result of network meta-analyses (OR 0.37 95% CrI 0.22–0.61), so is favor the synbiotics). For pairwise meta-analyses, ORs higher than 1 favor the row-defining treatment. (e.g., column 4 vs. row 1 in the upper right part of the table (EPN vs. synbiotics) is the result of pairwise meta-analyses (OR 2.50 95% CrI 1.50–4.60), so is favor the synbiotics). To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored. OR, odds ratio; CrI, credible interval; EPN, Enteral nutrition or adjuvant peripheral parenteral nutrition; TPN, Total parenteral nutrition.

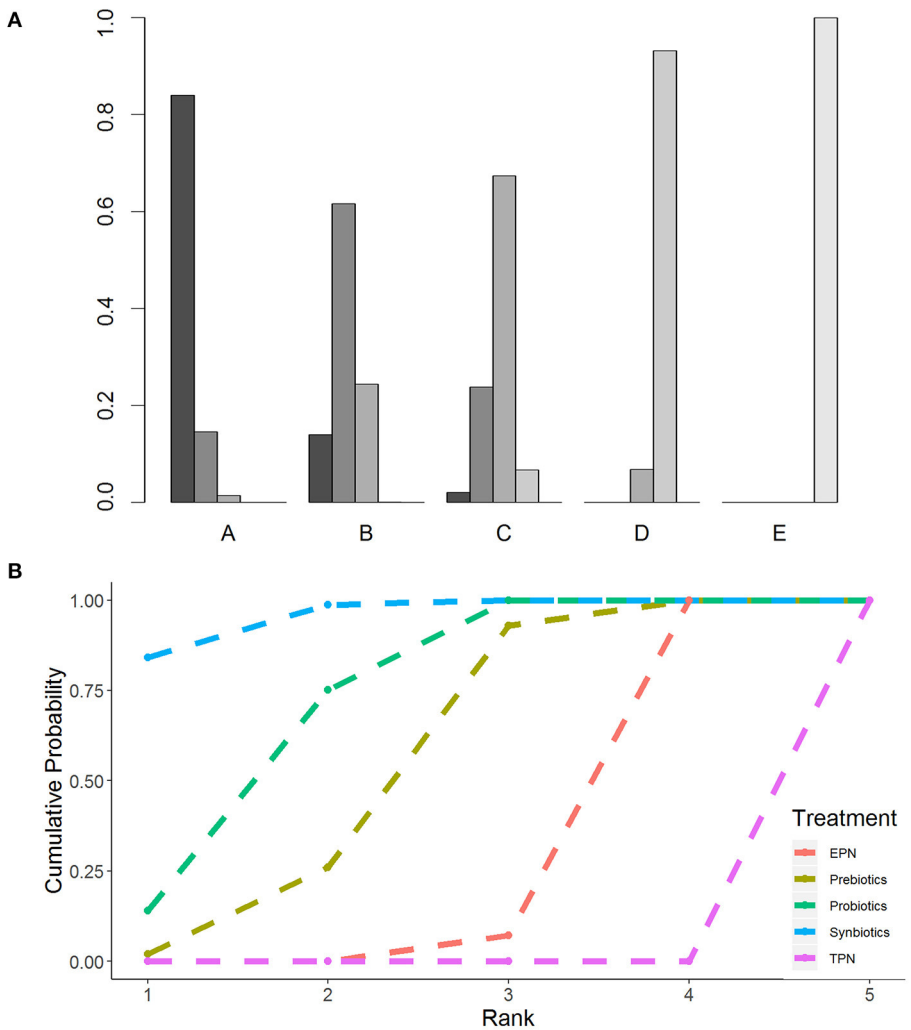

FIGURE 5 | Rankogram and SUCRA ranking curve for nosocomial infection. **(A)** Rankogram for nosocomial infection. A = Synbiotics. B = Probiotics. C = Probiotics. D = EPN. E = TPN. **(B)** SUCRA ranking for nosocomial infection. The number on the X-axis represents the rank. As the number goes up, the rating goes down. EPN, Enteral nutrition or adjuvant peripheral parenteral nutrition; TPN, Total parenteral nutrition.

CrI 0.51–3.87). In addition, we found that the heterogeneity and consistency in different disease subgroups were not statistically significant. Amongst RCTs over the last 10 years, high-quality studies and doses were used in our NMA. They were found to have no material impact on the relative treatment effects (**Supplementary File 13**).

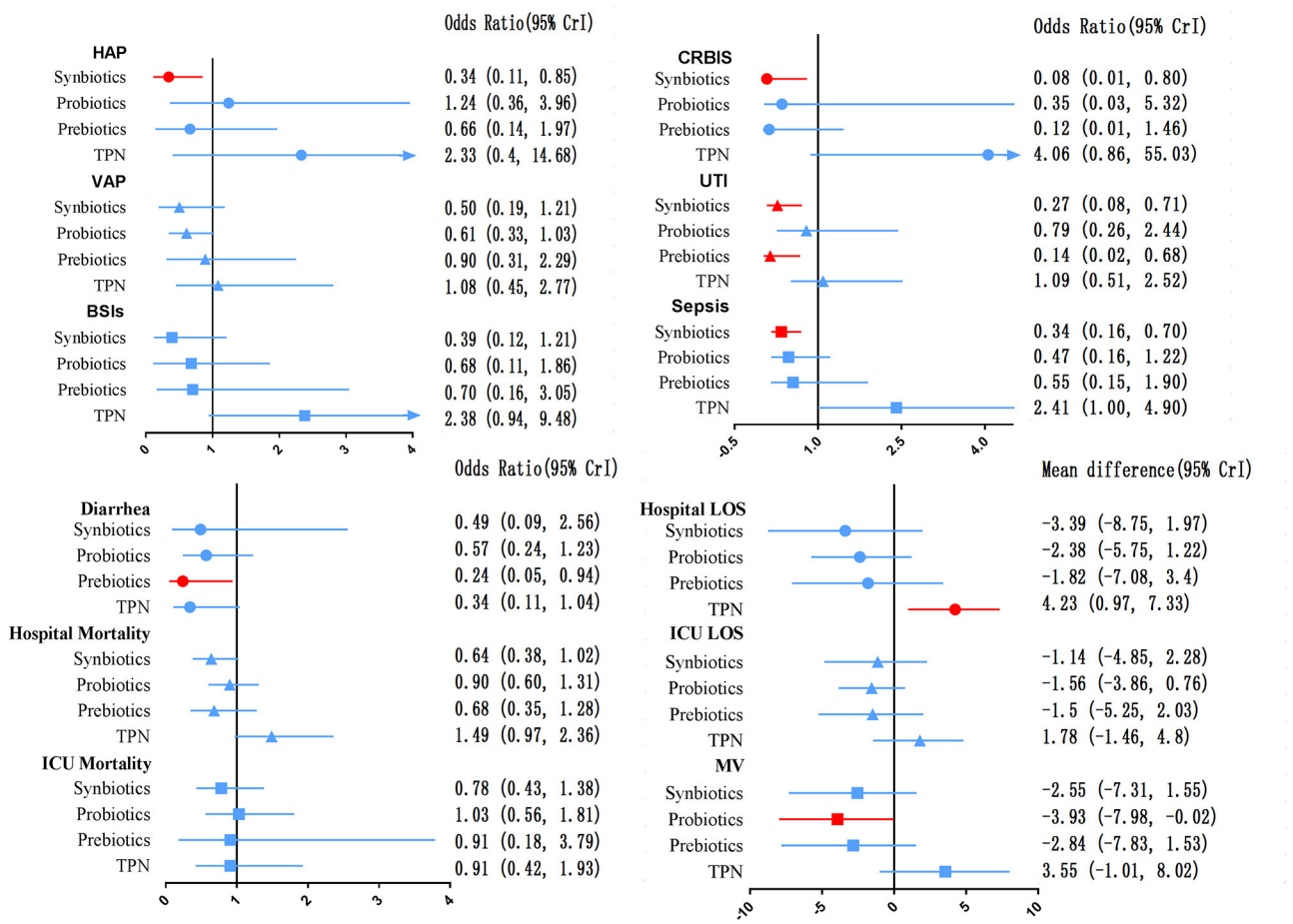

FIGURE 6 | Forest plot of the effect estimate for each active intervention vs. EPN on secondary outcomes. Estimates are presented as odds ratios (OR) and 95% CrI. OR < 1 favor the treatment. BSIs, Bloodstream infections; CrI, credible interval; CRIBS, Catheter-related bloodstream infection; EPN, Enteral nutrition or adjuvant peripheral parenteral nutrition; HAP, Hospital acquired pneumonia; TPN, Total parenteral nutrition; LOS, length of stay; MV, Duration of Mechanical ventilation; UTI, urinary tract infection; VAP, Ventilator-associated pneumonia.

The sensitivity analysis was evaluated based on high-quality studies, and the results did not change substantially (**Supplementary File 14**).

Risk of Bias Assessments and Grade for the Primary Outcome

In summary (**Supplementary File 4**), 1 (2%) of 55 rials was rated as high risk of bias, 23 (42%) trials were deemed moderate and 31 (56%) were considered low. We did not find publication bias for the network of outcomes, except duration of MV, hospital and ICU LOS (**Supplementary File 10**).

GRADE judgments for primary outcome were assessed and reported in **Table 6**. The certainty of evidence for the relative treatment effects of NI varied. It was high and moderate for most of the comparisons involving synbiotics, probiotics and prebiotics and low for most comparisons involving EPN and TPN. When subgroup analysis was performed, the GRADE between all comparisons and ranking of treatment was raised to at least moderate. Details of GRADE for secondary outcomes are presented in **Supplementary File 11**.

DISCUSSION

This study was based on the analysis of 55 RCTs enrolling 7,119 patients. Results indicated that synbiotic therapy was the best regimen in preventing NI in critically ill patients, while TPN exerted adverse curative effects amongst all the studied treatments. The sensitivity analyses for NI were consistent with the previous conclusions. Subgroup analysis based on diseases did not show significant heterogeneity between the included trials, and GRADE was moderate or high. These results further confirmed that the model was relevant and robust, making it applicable for use in clinical practice. Moreover, this analysis found that synbiotic therapy was the best regimen in improving HAP, CRBIS, UTI and sepsis. Probiotic and prebiotic treatments were the best regimens in shortening the duration of MV

TABLE 5 | Subgroup analyses for nosocomial infection in different populations.

	Overall patients		ICU patients		MV patients		SAP patients		Trauma patients		Nutrition therapy within 48 h		Nutrition therapy beyond 48 h	
	OR (95% CrI)	Rank	OR (95% CrI)	Rank	OR (95% CrI)	Rank	OR (95% CrI)	Rank	OR (95% CrI)	Rank	OR (95% CrI)	Rank	OR (95% CrI)	Rank
Synbiotics	**0.37 (0.22, 0.61)**	**1**	**0.45 (0.26, 0.71)**	**1**	0.41 (0.15, 1.07)	2	**0.12 (0.02, 0.81)**	**1**	**0.13 (0.013, 0.81)**	**1**	**0.40 (0.23, 0.68)**	**1**	0.18 (0.01, 2.50)	1
Probioticsn	**0.52 (0.34, 0.77)**	**2**	**0.54 (0.36, 0.78)**	**2**	**0.49 (0.24, 0.90)**	**1**	0.63 (0.20, 1.61)	3	0.38 (0.01, 12.54)	2	**0.52 (0.33, 0.77)**	**2**	0.52 (0.07, 2.99)	2
Prebiotics	0.65 (0.35, 1.15)	3	0.76 (0.41, 1.34)	3	0.70 (0.22, 1.80)	3	0.32 (0.06, 1.59)	2	0.66 (0.05, 5.99)	3	0.67 (0.35, 1.19)	3	1.00 (0.04, 22.95)	3
EPN	Reference	4	Reference	4	Reference	4	Reference	4	Reference	4	Reference	4	Reference	4
TPN	**2.29 (1.48, 3.67)**	**5**	**1.57 (1.01, 2.56)**	**5**	1.31 (0.51, 3.87)	5	**3.93 (1.74, 9.15)**	**5**	–	–	**1.78 (1.04, 3.16)**	**5**	**3.70 (1.16, 13.52)**	**5**
Number of studies	42		32		12		11		5		34		8	
Participants	6,215		5,414		3,726		996		290		5,641		601	

CrI, credible interval; EPN, Enteral nutrition or adjuvant peripheral parenteral nutrition; MV, Mechanical ventilation; OR, odds ratio; SAP, Severe acute pancreatitis; TPN, Total parenteral nutrition. Bold indicate statistical significance.

and preventing diarrhea, respectively. TPN was the worst in prolonging the hospital LOS.

Notably, this study differed from others in that it found no evidence that synbiotic therapies could reduce hospital and ICU mortality in critical patients (109). The mortality of critically ill patients was influenced by several complex risk factors (110). Probiotic and prebiotic therapy could not be fully absorbed by critically ill patients, so they may not have strong enough effects to reduce hospital and ICU mortality. Moreover, probiotic therapy did not significantly influence other clinical endpoints such as CRBIS, diarrhea and hospital LOS.

Results of subgroup analysis for the primary outcome were as follows. Firstly, subgroup analysis in different diseases showed that synbiotic therapy was the best treatment to improve NI in ICU patients. Conversely, TPN aggravated NI in ICU and SAP patients. These findings were consistent with the conclusions from NMA, thereby eliminating the effect of disease heterogeneity on the NMA outcome. Here, we focused on whether ICU patients can benefit from synbiotics. In addition, previous double-blind RCT and meta-analysis showed that TPN was associated with NI in ICU and SAP patients, which was consistent with the findings of this study. TPN therapy in ICU and SAP patients should be shortened as much as possible (25). Secondly, subgroup analysis in studies over the last 10 years and high quality showed that synbiotic therapy prevented NI, while TPN did not. These results were consistent with the standard analysis, including all studies in NMA, further confirming the robustness of the model and avoiding heterogeneity of the model. Thirdly, subgroup analysis in dosages of synbiotics showed no difference in the prevention of NI between the different doses. However, administered excessive synbiotic therapy not only failed to improve NI but also led to more infectious complications (16, 17). Hence, administered synbiotics in accordance with physiological requirements should be advocated to reduce the incidence of infectious complications. Fourthly, the subgroup of MV patients analysis showed that probiotic therapy can prevent NI. Only 3 out of a total of 12 studies administer synbiotics as the main intervention, and the patients involved were <10% of the total patients in this subgroup. Therefore, the power did not suggest that synbiotics can prevent NI. Finally, by adjusting the risk of NI and mortality through the initial nutrition therapy time, we found that synbiotics were associated with a reduction in NI among patients who were administered nutrition therapy within 48 h, and TPN were not associated with a reduction in NI, regardless of the time of nutrition therapy. This result suggests that we should administer initial enteral nutrition therapy within 48 h for critically ill adult patients (24, 25).

The primary finding of this study was inconsistent with results of previous studies. Many previous clinical trials, systematic reviews and meta-analysis efforts focused on whether symbiotics can improve NI in critically ill patients, and they rarely included probiotics. Moreover, those studies focused on the outcome of VAP (40, 111). In spite of promising data for probiotic use in reducing overall infections, the role of probiotics as a strategy to prevent VAP has been controversial (112). Recently, the

TABLE 6 | Result of GRADE for nosocomial infection.

	Nature of the evidence	Study limitations	Imprecision	Inconsistency	Indirectness	Publication bias	Confidence	Downgrading due to
A vs. B	Indirect estimated	No downgrade	No downgrade	No downgrade	No downgrade	No downgrade	High	–
A vs. C	Mixed estimated	Downgrade because >70% contribution from moderate Rob comparisons	No downgrade	No downgrade	No downgrade	No downgrade	Moderate	Study limitations
A vs. D	Mixed estimated	Downgrade because >70% contribution from moderate Rob comparisons	No downgrade	Downgrade because pair heterogeneity I^2 = 68.7%	No downgrade	No downgrade	Low	Study limitations Inconsistency
A vs. E	Indirect estimated	Downgrade because >70% contribution from moderate Rob comparisons	Downgrade because point estimate >1.0 but lower limit<0.80	No downgrade	No downgrade	No downgrade	Low	Study limitations Imprecision
B vs. C	Mixed estimated	No downgrade	No downgrade	No downgrade	No downgrade	No downgrade	High	Inconsistency
B vs. D	Mixed estimated	No downgrade	No downgrade	No downgrade Downgrade because sidesplitting p = 0.04143	No downgrade	No downgrade	Moderate	Inconsistency
B vs. E	Mixed estimated	No downgrade	No downgrade	No downgrade	No downgrade	No downgrade	High	–
C vs. D	Mixed estimated	Downgrade because >70% contribution from moderate Rob comparisons	Downgrade because point estimate >1.0 but lower limit<0.80	Downgrade because pair heterogeneity I^2 = 57.4%	No downgrade	No downgrade	Very low	Study limitations Imprecision Inconsistency
C vs. E	Indirect estimated	Downgrade because >70% contribution from moderate Rob comparisons	No downgrade	No downgrade	No downgrade	No downgrade	Moderate	Study limitations
D vs. E	Mixed estimated	No downgrade	No downgrade	Downgrade because pair heterogeneity I^2 = 76.4%	No downgrade	No downgrade	Moderate	Inconsistency
Ranking of treatments		Downgrade because >70% contribution from moderate Rob comparisons	No downgrade	Downgrade because global heterogeneity I^2 = 62.02%	No downgrade	No downgrade	Low	Study limitations Inconsistency

A, Synbiotic; B, Probiotic; C, Prebiotic; D, Enteral nutrition or adjuvant peripheral parenteral nutrition; E, Total parenteral nutrition.

results of the largest and most updated systematic review and meta-analysis demonstrated that probiotics are associated with a significant reduction in ICU-acquired infections and in the incidence of VAP. In addition, probiotics appeared to be more effective in reducing NI in patients at high risk of death than in patients at low and medium risk. However, such findings were limited by clinical heterogeneity and potential publication bias (42).

Although the mechanisms synbiotics were more effective than prebiotics and probiotics in preventing NI have not yet been clarified, the underlying mechanism areas discussed as follows: Firstly, synbiotics improve gut microbiota. Synbiotics not only increase the number of administered bacteria but also increase their genus groups and other microbiota, which could lead to the maintenance of gut microbiota (107). Secondly, synbiotics generate nutritional support for host epithelial cells. Synbiotic therapy had significantly increased levels of short-chain fatty acids are utilized mainly by intestinal epithelial cells as energy sources, The increased levels of short-chain fatty acids, especially acetate which might attenuate inflammation to reduce NI (60, 113). Thirdly, synbiotics maintain gut epithelial barrier. Increased levels of acetate and lactate might inhibit intraluminal toxins and maintain tight junctions (109). Finally, synbiotics regulate immune system function. Synbiotics regulates the innate and adaptive immune systems to reduce systemic inflammation and promote extra-intestinal organ function (109). These changes indicated that synbiotic therapy could have beneficial effects on reduce the development of NI (114, 115).

There were several strengths in this study. Firstly, this study was the first analysis using NMA to examine the effectiveness and determine the best choice of symbiotic regimen in improving NI in critically ill patients. This work helped us better assess the relative effects of treatment comparators in the absence of head-to-head trials. Secondly, our study is the most updated evaluation of the overall effects of symbiotic therapy in critically ill patients. It contained new suitable trials published on this topic since 1995 by focusing on NI. Thirdly, our study is the largest assessment of symbiotic therapy that included 55 RCTs published in both English and non-English languages from 24 countries, enrolling 7,119 patients. Fourthly, this study examined several relevant clinical outcomes in a heterogenous ICU patient population, including mixed ICU patients, MV patients, trauma patients, SAP patients and postoperative patients. Therefore, the results of this study helped reduce heterogeneity and potential publication bias and could be applied to a broad group of critically ill patients. Overall, all these factors increased the validity and robustness of our results.

Several limitations were still present in drawing strong treatment inferences. Firstly, the definitions of some diarrhea included our study were inconsistent because they are based on criteria of frequency, consistency (116), weight, duration and a combination of frequency and consistency. Such variations are rather vague and subject to different interpretations. There are at least 14 different definitions (117). Making those different definitions consistent is difficult. We were also unable to perform further grouping analysis because of the limited number of studies. Analogously, the definition of prebiotics more or less overlapped with the definition of dietary fiber. In addition, some studies did not provide the accurate definitions of study outcomes. We acknowledge potential misclassification and inconsistency, which is one of the reasons why we downgraded the GRADE of those secondary outcomes. Moreover, the variety of synbiotic strains and length of administration of therapy amongst the different trials weakened any possible clinical conclusions and recommendations. Given the limited number of studies evaluating each endpoint, we were unable to perform subgroup analysis for all clinical outcomes. A further limitation is that the quality of many comparisons was assessed as low or very low level of evidence for hospital LOS, ICU LOS, and duration of MV. Hence, the inferences from current findings were weakened. Lastly, the generalizability of results was limited to other populations as nearly 90% of all studies came from Asia and Europe countries. In addition to the above limitations, we acknowledge potential heterogeneity among critically ill patients in different trials. We have conducted subgroup analysis from many aspects such as different diseases populations, initial time of nutrition therapy, and strive to minimize heterogeneity.

A multicentre, concealed, randomized, stratified, blinded, controlled trial (111) to evaluate the effect of probiotics on VAP and other ICU-acquired infections in 2,650 critically ill patients is ongoing in Canada, USA and Saudi Arabia (clinical trials. gov. registration NCT02462590). REVISE Trials are also ongoing in North America, Australia and Saudi Arabia. The results of these trials will provide further information about the curative effect on symbiotics in the ICU.

CONCLUSION

This systematic review and NMA provide evidence that synbiotic therapy ranked first over probiotics, prebiotics, EPN and TPN to prevent NI in critically ill adult patients. Conversely, TPN therapy significantly increased NI in the critically ill compared with other therapies. Physicians in critical care and related disciplines should consider the use of synbiotics as an adjunctive therapy to improve NI amongst critically ill adult patients. At the same time, the duration of TPN alone should be reduced to decrease NI, especially in ICU and SPA patients. However, on the basis of current data, there is not currently sufficient evidence to make a final strong recommendation for synbiotic therapy to be utilized in the improvement of NI in the critically ill. Numerous questions remain unanswered about a variety of synbiotic strains, wide range of daily doses and duration of therapy; such topics can be addressed in future work.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CL, YY, and HQ had the idea for and designed the study. YH, LL, SL, and JX supervised the study. CL, ZG, JZ, HC, SM, AL, MM, DC, and CW did search clinical trials, study select, data extract, and statistical analysis. CL wrote the manuscript. All authors contributed to acquisition, analysis, interpretation of data, revised the report, and approved the final version before submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.693188/full#supplementary-material

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