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;
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 aden 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,
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.
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, 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 \([\log_{10} \text{CFUs}/\text{g of feces}]\) (59–61). Therefore, we defined the dose of probiotics that was >2 \(10^{10} \text{CFU} \text{per day as high dose and the rest as moderate to low doses.} \)

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 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...
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 |
| 2 | Kudsk et al. (63) | 1996 | America | ICU patients with severe trauma | SC/OP | 33 | 33 (3) | 61 | NR | NR | EN |
| 3 | Bleichner et al. (64) | 1997 | France | Critical patients in ICU | MC/DB | 64 | 61.6 (12.3) | 70 | NR | NR | Probiotics+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 |
| 5 | Jain et al. (27) | 2004 | United of kingdom | Critical patients in ICU | SC/DB | 45 | 72 (11.1) | 58 | NR | NR | Symbiotics+EN |
| 6 | Lu et al. (66) | 2004 | China | Critical patients with severe burns | SC/DB | 20 | 36.05 (5.16) | 85 | NR | NR | Symbiotics+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 |
| 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 |
| 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 |
| 10 | Morrow et al. (69) | 2005 | America | MV patients | SC/DB | 19 | 51 | 71 (43.7) | 51 | 12 (6.7) | NR | 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 | Symbiotics+EN |
| 12 | Petrov et al. (71) | 2006 | Russia | Severe acute pancreatitis patients with organ failure | SC/OP | 35 | 55.9 (18) | 83 | 19.36 (2.1) | NR | Placebo+EN |
| 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 | Symbiotics+EN |
| 14 | Abdulmeguid and Hassan (73) | 2007 | Greece | MV > 2 days critical patients in ICU | SC/OP | 40 | 35 (20.8) | 58 | 12 (8.4) | NR | EN |
| 15 | Alberda et al. (74) | 2007 | Canada | ICU patients | SC/DB | 10 | 60.4 (17.9) | 50 | 18.2 (4.2) | NR | Probiotics+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 |
| 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 |

(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 | Symbiotics+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 | Symbiotics+EN       |
|    |        |      |         |          |        | 11 | NR | NR | Prebiotics+EN | EN         |
|    |        |      |         |          |        | 144 | 59.0 (15.5) | 57 | 8.4 (4.5) | 1.9 | EN                |
| 20 | Besselink et al. (53) | 2008 | Netherlands | Patients with predicted severe acute pancreatitis | MC/DB | 152 | 60.4 (16.5) | 59 | 8.6(4.4) | 2.1(2.0) | Probiotics+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 (4.07) | 64 | NR | NR | Probiotics+EN       |
| 22 | Klarin et al. (80) | 2008 | Sweden | Critical patients in ICU | MC/DB | 22 | 65.5 (44.44) | 59 | 22 | 16.3 | Symbiotics+EN       |
|    |        |      |         |          |        | 22 | 64 (60.37) | 59 | 11 | 20 | 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 | EN | Placebo+EN          |
|    |        |      |         |          |        | 25 | 41.1 (11.3) | NR | ≥8 | EN | TPN                |
| 24 | Giamarellos- Bourboulis et al. (82) | 2009 | Greece | SICU patients with severe multiple injuries | MC/DB | 36 | 55.9 | NR | 19.36 | NR | Symbiotics+EN       |
| 25 | Knight et al. (26) | 2009 | United of kingdom | MV patients | SC/DB | 130 | 49.5 (19.6) | 62 | 17 (8.1) | NR | Symbiotics+EN       |
|    |        |      |         |          |        | 129 | 50.0 (18.5) | 62 | 17 | 7.4 | 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 | Placebo+EN          |
| 27 | Barraud et al. (84) | 2010 | France | MV patients | SC/DB | 87 | 59.1 (15.9) | 39 | NR | 9 (4.6) | TPN |
|    |        |      |         |          |        | 30 | 50.83 (12.4) | 73 | NR | NR | Probiotics+EN       |
|    |        |      |         |          |        | 80 | 61.8 (15.5) | 44 | NR | 9.7 | 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       |
| 29 | Morrow et al. (29) | 2010 | America | MV patients | SC/DB | 73 | 67.5 (31.11) | 33 | 22.7 | 7.5 | NR | Placebo+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 | 562 (19.4) | 44 | 27.7 | 8.3 | NR | Symbiotics+EN       |
| 31 | Tan et al. (87) | 2011 | China | ICU patients with severe TBI | SC/DB | 26 | 40.5 (13.0) | 73 | 14.5 (3.6) | 6.5 | NR | Probiotics+EN       |
|    |        |      |         |          |        | 26 | 40.8 (12.8) | 81 | 14.3 | 3.6 | 6.3 | EN                |
| 32 | Hayakawa et al. (88) | 2012 | Japan | MV patients | SC/OP | 31 | 74 (14.4) | 51 | NR | NR | Symbiotics+EN       |
|    |        |      |         |          |        | 16 | 75 (7) | 75 | NR | NR | EN                |
| 33 | Malan et al. (89) | 2012 | America | Critical patients in SICU | SC/DB | 36 | 60 | 59 | 16.7 | NR | Probiotics+EN       |

(Continued)
| ID  | Author et al. | 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         | Symbiotics + EN |
|     |                |      |         |                                                                            |        | 28 | NR            | 37       | 8.6 (4.9)       | NR         | Prebiotics + EN |
|     |                |      |         |                                                                            |        | 32 | NR            | 37       | 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              | ≥8         | NR            |
|     |                |      |         |                                                                            |        | 25 | ≥8            | NR       | EN              |            | Prebiotics + EN |
|     |                |      |         |                                                                            |        | 22 | ≥8            | NR       | EN              |            | TPN           |
| 36  | Elke et al. (92) | 2013 | Germany | ICU patients with severe sepsis or septic shock                           | SC/OP  | 32 | NR            | 62       | 20 (5.8)        | 7 (3.6)    | EN            |
| 37  | Tan et al. (93) | 2013 | China   | SICU patients with severe TBI                                            | SC/DB  | 26 | 40.5 (13.0)   | 73       | 14.8 (3.6)      | NR         | Prebiotics + EN |
|     |                |      |         |                                                                            |        | 26 | 40.8 (12.8)   | 81       | 14.3 (3.6)      | NR         | 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)    | 12.63 (3.67)| NR            |
|     |                |      |         |                                                                            |        | 61 | 43.7 (13.7)   | 52       | 13.27 (2.88)    | 12.55 (2.6) | NR            |
|     |                |      |         |                                                                            |        | 60 | 41.7 (11.4)   | 57       | 14.3 (3.6)      | 12.55 (2.6) | EN            |
| 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)    | Symbiotics + EN |
|     |                |      |         |                                                                            |        | 43 | 70 (14.07)    | 68       | 22 (5.9)        | 6 (2.2)    | 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)| Prebiotics + 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             | ≥8         | NR            |
| 42  | Fu et al. (97) | 2015 | China   | Patients with severe acute pancreatitis                                  | SC/OP  | 36 | 48.9 (12.2)   | 53       | ≥8             | ≥8         | NR            |
|     |                |      |         |                                                                            |        | 19 | 42.0 (16.5)   | 53       | 11.4 (4.9)      | NR         | Placebo + EN  |
| 43  | Kim et al. (98) | 2015 | South Korea | ICU patients after living donor liver transplantation                   | SC/OP  | 17 | 52 (7)        | 88       | 12.3 (5.1)      | NR         | TPN           |
|     |                |      |         |                                                                            |        | 19 | 52 (5.5)      | 95       | NR             | NR         | EN            |
| 44  | Rongrungruang et al. (99) | 2015 | Thailand | MV patients                                                                | SC/OP  | 75 | 68.95 (18.45) | 60       | 19.98 (6.89)    | NR         | Prebiotics + EN |
|     |                |      |         |                                                                            |        | 75 | 73.9 (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         | TPN           |
|     |                |      |         |                                                                            |        | 40 | 41.56 (15.10) | 53       | NR             | NR         | Placebo + EN  |
| 46  | Malik et al. (101) | 2016 | Malaysia | Critical patients in ICU                                                | SC/DB  | 24 | 60 (14.4)     | 67       | 22.12 (6.0)     | NR         | Prebiotics + 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         | TPN           |
|     |                |      |         |                                                                            |        | 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)     | 16.6 (4.3) | Prebiotics + EN |
|     |                |      |         |                                                                            |        | 117 | 54.8 (17.9)   | 56       | 16.6 (4.3)     | EN         | TPN           |
| 49  | Alberda et al. (103) | 2018 | Canada  | Critical patients in ICU                                                | SC/OP  | 16 | 59.9 (15.6)   | 75       | 25.5 (5.39)    | 25.9 (9.70) | Prebiotics + EN |
|     |                |      |         |                                                                            |        | 16 | 57.5 (15.0)   | 63       | NR             | NR         | EN            |
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 probiotic 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, 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. Symbiotic 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, symbiotic therapy was more effective than EPN, and the results of the network were OR 0.24; 95% CrI 0.05–0.94. By contrast, TPN was worse than EPN on shortening of hospital LOS (MD −3.93; 95% CrI −7.98 to −0.02). In terms of preventing the efficacy of diarrhea, probiotics were more effective than EPN (OR 2.29; 95% CrI 1.48–3.67). Figure 5 shows the SUCRA ranking curve of NI. Symbiotic treatment was the best choice in preventing NI, whereas TPN was the worst.

### 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.
| 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              |
| 2  Kudsk et al. (63)                      | ICU patients with severe trauma                                  | 27 | TPN          | Isonitrogenous isocaloric                                                                | Mean 1,400 kcal/day NR         |
| 3  Bleichner et al. (64)                  | Critical patients in ICU                                         | 64 | 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 | Symbiotics+EN | Fermented milk (Lactobacillus johnsonii)                                               | Fermented milk 240 ml QD       |
|                                           |                                                                  | 10 | EN           | **Probiotics (Trevis™):** L. acidophilus, L. bulgaricus, Bifidobacterium lactis Bb-12, Streptococcus thermophilus | NR                            |
|                                           |                                                                  | 45 | Symbiotics+EN | **Prebiotics:** oligofructose **EN:** NR                                                | Probiotic 4 × 10⁹ cfu TID      |
|                                           |                                                                  | 45 | Placebo+EN   | **Placebo:** Sucrose powder **EN:** NR                                                  | Prebiotic 7.5 g BID           |
| 5  Jain et al. (27)                       | Critical patients in ICU                                         | 45 | Symbiotics+EN | **Probiotics:** Pediococcus pentosaceus, Lactobacillus paracasei subsp paracasei, Lactobacillus plantarum, L. lactis, L. paracasei subsp paracasei, Streptococcus thermophilus | Probiotic 4 × 10¹⁰ cfu QD      |
|                                           |                                                                  | 51 | EN           | **Prebiotics:** Proviva (L. plantarum 299v)                                             | 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                            |
| 8  Klarin et al. (68)                     | Critical patients in ICU                                         | 50 | TPN          | Harris-Benedict formula                                                                 | 125–146 kJ/kg                 |
|                                           |                                                                  | 8  | Probiotics+EN | **Probiotics:** Lactobacillus plantarum 299v                                           | Probiotic 5 × 10¹⁰ cfu Q6 3 days |
|                                           |                                                                  | 7  | EN           | **Prebiotics:** Probiotics: 2.5 × 10⁹ cfu QDF                                           | NR                            |
|                                           |                                                                  | 52 | Probiotics+EN | **Prebiotics:** Betaglucan, Inulin, Pectin, Resistant starch **EN:** Nutrison Fibre       | NR                            |
| 9  McNaught et al. (28)                   | Critical patients in ICU                                         | 51 | EN           | EN                                                                                      | NR                            |
|                                           |                                                                  | 19 | Probiotics+EN | Lactobacillus GG                                                                        | 1 × 10⁹ cfu BID               |
|                                           |                                                                  | 21 | Placebo+EN   | Inactive plant starch inulin                                                             | Prebiotic 4 × 10⁹ cfu QD       |
| 10 Morrow et al. (69)                     | MV patients                                                     | 35 | Symbiotics+EN | Syntobi 2000 Forte **Probiotics:** Pediococcus pentosaceus 5–33:3, L. paracasei subsp paracasei 19, L. plantarum 2:362 | Prebiotic 10 g QD             |
|                                           |                                                                  | 30 | Placebo+EN   | **Placebo:** Peptamen                                                                    | Daily 30 kcal/kg and 1.5 g/kg of protein (ideal body weight) |
| 11 Kotzampassi et al. (70)                | SICU patients with severe multiple trauma                       | 35 | EN           | Peptamen                                                                                 |                               |
|                                           |                                                                  | 34 | TPN          | 10% dextrose solution, 10% amino acid solution, and 10% fat emulsion                     |                               |

(Continued)
| Author | Diseases | N | Intervention | Details of intervention | Dose or volume of intervention |
|--------|----------|---|-------------|-------------------------|-------------------------------|
| 13 Spindler-Vesel et al. | SICU patients with severe multiple trauma | 26 | Symbiotics+EN | Symbiotic 2000 Probiotics: Lactobacillus: Pedicoccus pentosaceus 5–33:3, Lactococcus rafinolactis 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 | 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. | MV > 2 days critical patients in ICU | 40 | EN | NR | NR |
| 40 | TPN | Identical amounts of fat, carbohydrate, and protein. | |
| 15 Alberda et al. | Critical 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. | 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. | Severe acute pancreatitis patients with organ failure | 15 | Probiotics+EN | Multifiber: Soluble fibers and insoluble fibers | 2.4 g per day |
| 15 | EN | No prebiotics, no placebo | 2,000 kcal/d |
| 18 Otah et al. | Severe acute pancreatitis patients with organ failure | 33 | Symbiotics+EN | Synbiotic 2000 Forte Probiotics: Pedicoccus pentosaceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei subsp 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. | Critical patients in ICU | 15 | Symbiotics+EN | Synbiotic 2000 Forte Probiotics: Pedicoccus pentosaceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei subsp 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 | Probiotic 10^10 cfu totally daily |
| 20 Besselink et al. | 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 10^6 cfu BID |
| 144 EN | Nutrison Multi Fibre | NR |
| 21 Forestier et al. | Critical patients in ICU | 102 | Probiotics+EN | Probiotics: Lactobacillus casei rhamnosus | 10^6 cfu BID |
| 106 Placebo+EN | Placebo: Growth medium without bacteria | NR |
| Author                  | Diseases                                                               | N  | Intervention | Details of intervention                                                                 | Dose or volume of intervention                                                                 |
|------------------------|------------------------------------------------------------------------|----|--------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Klarin et al. (80)     | Critical patients in ICU                                               | 22 | Symbiotics + 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 | Probiotics: Oatmeal                                                                      | Same oatmeal gruel mixed with lactic acid                                                      |
| Dooley 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                                                |
| Giamarellos-Bourboulis et al. (82) | SICU patients with severe multiple injuries                           | 36 | Symbiotics + EN | Syngiotic 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                                               |
| Knight et al. (26)     | MV patients                                                            | 130| Symbiotics + EN | Syngiotic 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                                             |
| 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                                                    |
| 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^{11} cfu QD EN: 30–35 kcal/kg                                             |
|                        |                                                                        | 80 | Placebo + EN | Placebo: Excipient EN: Fresubin                                                          | Placebo: NR EN: 30–35 kcal/kg                                                                |
| 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 kilogram                  |
| Morrow et al. (29)     | MV patients                                                            | 73 | Probiotics + EN | Probiotics: Lactobacillus rhamnosus GG EN: NR                                            | Probiotics: 2 × 10^{9} cfu BID                                                               |
|                        |                                                                        | 73 | Prebiotics + EN | Probiotics: Inulin EN: NR                                                                | BID                                                                                            |
| Ferrie and Daley (88)  | Critically ill patients with diarrhea                                  | 18 | Symbiotics + EN | Probiotics: Lactobacillus rhamnosus GG Prebiotics: inulin powder EN: standard feeding formula, which is a 1-calorie per mL oat fiber-containing formula | Probiotics: 10^{10} cfu QD Prebiotic: 280 mg QD                                              |

(Continued)
| Author          | Diseases                                     | N  | Intervention                        | Details of intervention                                                                 | Dose or volume of intervention |
|-----------------|----------------------------------------------|----|-------------------------------------|------------------------------------------------------------------------------------------|-------------------------------|
| Tan et al. (87) | ICU patients with severe TBI                 | 26 | Probiotics+EN                       | Prebiotics: Inulin powder **EN**: standard feeding formula, which is a 1-calorie per mL oat fiber-containing formula | Prebiotic: 280 mg QD          |
|                 |                                              |    |                                     | Prebiotic: 280 mg QD per day **EN**: 30 kcal/kg body weight/day                            |                               |
| 31              |                                              |    |                                     |                                                                                          |                               |
| Hayakawa et al. (88) |                                              | 31 | Synbiotics+EN                       | Probiotics: (Yakult): 1 x 10⁸ cfu/g Bifidobacterium breve strain Yakult, 1 x 10⁹ cfu/g Lactobacillus casei strain Shirota **Prebiotics**: galactooligosaccharides **EN**: Medef (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 **EN**: According to the patient's requirements |
| 32              | MV Patients                                   | 31 | Synbiotics+EN                       | Prebiotics: 10⁹ cfu per day **EN**: 30 kcal/kg body weight/day                            |                               |
|                 |                                              |    |                                     |                                                                                          |                               |
| Malian et al. (89) | Critical patients in SICU                   | 36 | Probiotics+EN                       | Probiotics: Lactobacillus GG **EN**: NR                                                  | NR                            |
| 33              |                                              |    |                                     | Placebo: **NR** **EN**: **NR**                                                             |                               |
| Plaudis et al. (90) | Severe acute pancreatitis patients with organ failure | 30 | Synbiotics+EN                       | Probiotics: 10 g BID **EN**: 2,500 kcal/day                                              |                               |
|                 |                                              |    |                                     | Prebiotic: 10 g BID **EN**: According to the patient's requirements **EN**: NR              |                               |
|                 |                                              |    |                                     |                                                                                          |                               |
| Cui et al. (91) | Severe acute pancreatitis patients with organ failure | 23 | Probiotics+EN                       | Prebiotics: Bifidobacterium **EN**: Peptisorb, Nutrison Fibre                             | Prebiotics: 10 g BID **EN**: 2,500 kcal/day |
| 35              |                                              |    |                                     |                                                                                          |                               |
| Elke et al. (92) | ICU patients with severe sepsis or septic shock | 328| EN                                   | **NR**                                                                                  | **NR**                        |
| 36              |                                              |    |                                     |                                                                                          |                               |
| Tan et al. (93) | SICU patients with severe TBI                | 26 | Probiotics+EN                       | **Prebiotics**: Golden Bifid: 0.5 x 10⁸ cfu/g Bifidobacterium longum, 0.5 x 10⁷ cfu/g Lactobacillus bulgaricus, 0.5 x 10⁷ cfu/g Streptococcus thermophilus **EN**: Standard formula | **Prebiotics**: 0.5 g TID **EN**: 2 g proteins/kg/d and 35 kcal/kg/d |
|                 |                                              |    |                                     |                                                                                          |                               |
| Wang et al. (94) | ICU patients with severe acute pancreatitis  | 62 | Probiotics+EN                       | **Prebiotics**: Bacillus subtilis 1.8 x 10⁸ cfu/g, Enterococcus faecium 2.0 x 10⁸ cfu/g **EN**: PEPTISORB | **EN**: 2 g proteins/kg/d and 35 kcal/kg/d |
| 38              |                                              |    |                                     |                                                                                          |                               |

(Continued)
| Author                   | Diseases                                | N  | Intervention | Details of intervention                                                                 | Dose or volume of intervention |
|-------------------------|-----------------------------------------|----|--------------|-----------------------------------------------------------------------------------------|-------------------------------|
| Lopez de Toro et al.    | ICU patients with multi-organ failure   | 60 | TPN          | TPN                                                                                     | 2 g proteins/kg/d and 35 kcal/kg/d, A ratio of 120:1 of non-protein calories-to-nitrogen |
| Sanaie et al. (96)      | Critical patients in ICU                | 46 | Synbiotics+EN| Probiotics (Drink Simbiotic): streptococcus Thermophilus, lactobacillus bulgaricus, Lactobacillus casei, lactobacillus acidophilus, bifidobacterium, Escherichia coli, coliformes Prebiotics: NR | Max 4.8 × 10⁹ cfu/ml |
| Zhu et al. (34)         | Severe acute pancreatitis patients with organ failure | 20 | Probiotics+EN| Probiotics: Clostridiun Butyricum (miiyarisan) EN: NR                                      | Probiotics: 9.0 × 10⁹ cfu BID EN: Energy requirements 25–30 kcal/kg and protein 1.2–1.5 g/kg. |
| Fu et al. (97)          | Patients with severe acute pancreatitis | 36 | Probiotics+EN| Probiotics: live combined bacillus subtilis and enterococcusfaaecium EN: Peptisorb, Nutrison Fibre | Energy requirements 25–30 kcal/kg and protein 1.2–1.5 g/kg. |
| Kim et al. (98)         | ICU patients after living donor liver transplantation | 17 | EN          | Mediwell RTH 500                                                                         | 0.7 × 10⁶ cfu BID The same capsule type and amount |
| Rongrungruang et al.    | MV patients                             | 75 | Probiotics+EN| Probiotics: Lactobacillus casei (Yakult) (Shirota strain) EN: NR                          | NR                           |
| Fan et al. (100)        | NICU patients with severe TBI           | 80 | EN          | Nutrison Fibre                                                                          | NR                           |
| 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 (semi elemental formula), and Novasource Renal (electrolyte and fluid restriction). | NR                           |
| Zarinfar et al. (102)   | MV patients                             | 30 | Probiotics+EN| Probiotics: Lactobacillus GG Placebo: NR                                                | 3 g BID EN                        |

Continued...
| Author | Diseases | N  | Intervention | Details of intervention | Dose or volume of intervention |
|--------|----------|----|--------------|-------------------------|--------------------------------|
| Zeng et al. (32) | MV patients | 118 | Probiotics+EN | Probiotics: Medilac-S; Bacillus subtilis 4.5 × 10^9 cfu/g and Enterococcus faecalis 0.5 × 10^9 cfu/g. EN: NR | Probiotics: 0.5 g TID EN: NR |
| Alberda et al. (103) | Critical patients in ICU | 16 | Probiotics+EN | Probiotics: Lactobacillus casei (Danactive) | 1 × 10^10 cfu BID |
| Faziaty et al. (104) | ICU patients with multiple trauma | 20 | Prebiotics+EN | Prebiotics: b-glucon EN: high-protein enteral diet (20% protein, 30% lipid, and 50% carbohydrate) | 3 g QD 25–30 kcal/kg |
| Kooshki et al. (105) | MV patients | 30 | Prebiotics+EN | Prebiotics: Ferugreek seed powder EN: NR | 3 g BID |
| Reigner 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. |
| Shimizu et al. (107) | Patients MV for ≥72 h and diagnosed sepsis | 35 | Synbiotics+EN | Probiotics: Yakult BL Seichoysaku: 1 × 10^9 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 |
| Tuncay et al. (108) | Critical patients in NICU | 23 | Prebiotics+EN | Prebiotics: Fructo-oligosaccharides (Jevity, 1 kcal/ml) EN: Standard formula (Osmolite, 1 kcal/ml) | Prebiotics: 5.3 g QD 1 g/kg/day EN: 30–40 ml/kg/day 1 g/kg/day and 30–40 ml/kg/day |
| 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 cfu 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.
| 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 NR | NR NR NR | 14.3 (5.0) NR NR NR |
| TPN          | 4/27 NR NR NR NR NR NR NR NR NR NR | NR NR NR | 19.3 (7.3) NR NR NR |
| 2 EN         | 16/33 2/33 5/33 8/33 NR NR 2/33 NR 25.7 (8.8) 7.7 (2.8) 3.9 (2.3) |
| TPN          | 13/19 4/19 8/19 4/19 NR 0/19 NR 34.9 (6.0) 15.7 (4.9) 9.0 (4.2) |
| Probiotics+EN| NR NR NR NR NR NR NR NR NR NR | NR NR NR | 18/64 NR NR NR |
| Placebo+EN   | NR NR NR NR NR NR NR NR NR NR | NR NR NR | 24/64 NR NR NR |
| 4 Synbiotics+EN | 5/10 0/10 3/10 0/10 NR NR 2/10 NR 11.1 (10) 7.7 (10.3) 3.9 (2.3) |
| Placebo+EN   | 10/10 NR NR NR NR NR NR NR NR NR NR | NR NR NR | 22 (37.0) 7.7 (2.8) 3.9 (2.3) |
| 3 Probiotics | NR NR NR NR NR NR NR NR NR NR | NR NR NR | 25.7 (8.8) 7.7 (2.8) 3.9 (2.3) |
| Placebo     | NR NR NR NR NR NR NR NR NR NR | NR NR NR | 34.9 (6.0) 15.7 (4.9) 9.0 (4.2) |
| 5 Synbiotics+EN | 16/33 5/33 8/33 NR NR NR NR NR NR NR | 15 (12.5) 5 (8.1) 4 (3.7) NR |
| Placebo+EN   | 26/45 8/45 3/45 13/45 NR NR NR NR NR NR | 15 (12.5) 5 (8.1) 4 (3.7) NR |
| 6 Synbiotics+EN | 8/20 2/20 3/20 4/20 NR NR NR NR NR NR | 15 (12.5) 5 (8.1) 4 (3.7) NR |
| Placebo+EN   | 11/20 NR NR NR NR NR NR NR NR NR NR | 15 (12.5) 5 (8.1) 4 (3.7) NR |
| 7 EN         | NR NR NR NR NR NR NR NR NR NR | NR NR NR | 18/50 7.5 (20.5) 9.5 (15.2) |
| TPN          | NR NR NR NR NR NR NR NR NR NR | NR NR NR | 30.2 NR NR NR |
| Probiotics+EN| 6/8 5/8 0/8 3/8 2/8 NR NR 2/8 NR 12 (24.4) NR NR |
| EN           | 5/7 2/7 3/7 3/7 1/7 NR NR 2/7 NR 11 (33.3) NR NR |
| Probiotics+EN| 21/52 NR NR NR NR NR NR NR NR NR | 25.7 (8.8) 7.7 (2.8) 3.9 (2.3) |
| EN           | 22/51 NR NR NR NR NR NR NR NR NR | 25.7 (8.8) 7.7 (2.8) 3.9 (2.3) |
| 10 Probiotics+EN | 2/19 0/19 2/19 0/19 NR NR NR NR NR NR | 15 (12.5) 5 (8.1) 4 (3.7) NR |
| Placebo+EN   | 7/21 NR 10/21 NR NR NR NR NR NR NR NR | 15 (12.5) 5 (8.1) 4 (3.7) NR |
| 11 Synbiotics+EN | 17/35 19/35 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 20/30 13/30 12/30 10/30 NR 10/30 NR | 41.3 (20.5) 29.7 (16.15) |
| 12 EN        | 7/35 2/35 NR 0/35 2/35 NR NR 6/35 NR 2/35 NR NR NR |
| TPN          | 25/34 2/34 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 (9.4) 11 (8.3) NR NR |
| Prebiotics+EN| 17/29 12/29 NR 2/29 0/29 0/29 NR NR 2/29 2/29 NR | 12 (9.4) 11 (8.3) NR NR |
| EN           | 29/58 22/58 NR 2/58 2/58 1/58 NR NR 3/58 3/58 NR | 12 (9.4) 11 (8.3) NR NR |
| Prebiotics+EN| 2/19 NR NR NR NR NR NR NR NR NR NR NR | 12 (9.4) 11 (8.3) NR NR |
| 14 EN        | 14/40 NR NR NR NR NR NR NR NR NR NR NR | 12 (9.4) 11 (8.3) NR NR |
| TPN          | 20/40 NR NR NR NR NR NR NR NR NR NR NR | 12 (9.4) 11 (8.3) NR NR |
| Probiotics+EN| 0/10 NR NR NR NR NR NR NR NR NR NR NR NR | 12 (9.4) 11 (8.3) NR NR |
| EN           | 0/18 NR NR NR NR NR NR NR NR NR NR | 12 (9.4) 11 (8.3) NR NR |
| Prebiotics+EN| 3/15 NR NR NR NR NR NR NR NR NR NR NR | 12 (9.4) 11 (8.3) NR NR |
| 17 EN        | 3/15 NR NR NR NR NR NR NR NR NR NR | 12 (9.4) 11 (8.3) NR NR |
| Prebiotics+EN| 9/33 2/33 NR NR 3/33 3/33 NR 2/33 NR 14.9 NR NR |
| Prebiotics+EN| 15/33 4/29 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 NR | 14 (16.3) NR NR |
| Prebiotics+EN| 4/10 NR NR NR NR NR NR NR NR NR NR NR | 14 (16.3) NR NR |
| 20 Probiotics+EN | 46/152 24/152 NR 32/152 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 NR 28/144 NR 9/144 NR | 23.5 (25.9) 3 (9.3) NR |
| Probiotics+EN| 24/102 NR NR NR NR NR NR NR NR NR NR | NR NR NR |
| Prebiotics+EN| 24/106 NR NR NR NR NR NR NR NR NR NR | NR NR NR |
| Placebo+EN   | 15/106 NR NR NR 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 (14.4) 4.4 (12.0) NR NR |
| Prebiotics+EN| 16/22 9/22 NR 3/22 3/22 1/22 NR NR 2/22 2/22 NR | 5.5 (14.4) 4.4 (12.0) NR NR |
| 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 |
| Prebiotics+EN| NR NR NR NR NR NR NR NR NR NR NR NR | NR NR NR |
| 24 Synbiotics+EN | NR NR 15/36 5/36 6/36 5/36 NR NR NR | 5 (5.9) 6 (5.1) NR NR |
| EN           | NR NR 16/36 13/36 NR 11/36 13/36 NR NR NR | NR NR NR |
| Synbiotics+EN | 12/130 NR 12/130 NR NR NR NR NR NR NR NR | 19 (20.7) 6 (5.9) 5 (5.1) NR |

(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 | ICU | MV |
| Placebo+EN   | 17/129 | NR | 17/129 | NR | NR | NR | NR | 9/129 | 42/129 | 34/129 | 18 (18.52) | 7 (8.14) | 5 (5.92) | 693188 |
| 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      | NR | NR | NR | NR | NR | NR | NR | NR | 5/20 | NR | 7.3 (5.7) | 6 (5.2) |
| 28 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | 3/25 | NR | 8.1 (4.4) | 6.7 (5.25) |
| 29 Probiotics+EN | 13/73 | NR | 13/73 | NR | NR | NR | NR | 46/73 | 13/73 | NR | 21.7 (17.4) | 14.8 (11.8) | 9.6 (7.2) |
| Prebiotics   | NR | NR | NR | NR | NR | NR | NR | NR | 0/26 | NR | 10.7 (7.3) | NR |
| 30 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | 1/25 | NR | 10.4 (3.9) | NR |
| 31 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | 12/22 | NR | 25.8 (6.4) | NR |
| EN           | 15/26 | NR | 1/7 | 13/19 | NR | 1/26 | 0/26 | NR | 5/26 | NR | 14 (2) | 14 (2) |
| 32 Synbiotics+EN | 5/31 | NR | 5/31 | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 3/16 | NR | 3/16 | NR | NR | NR | NR | NR | NR | NR | NR |
| 33 Synbiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Prebiotics   | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| 34 Synbiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 12/32 | NR | 7/32 | NR | 1/32 | NR | NR | NR | NR | NR | NR |
| 35 Prebiotics | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 5/25 | NR | 1/25 | NR | 3 (1.2) | NR | NR | NR | NR | NR | NR |
| 36 EN         | 183/328 | NR | 183/328 | NR | NR | NR | NR | NR | NR | NR | NR |
| TPN          | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| 37 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| 38 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 13/61 | NR | 13/61 | NR | NR | NR | NR | NR | NR | NR | NR |
| 39 Synbiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 24/60 | NR | 24/60 | NR | NR | NR | NR | NR | NR | NR | NR |
| 40 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 13/43 | NR | 13/43 | NR | NR | NR | NR | NR | NR | NR | NR |
| 41 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 5/20 | NR | 5/20 | NR | NR | NR | NR | NR | NR | NR | NR |
| 42 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 6/19 | NR | 6/19 | NR | NR | NR | NR | NR | NR | NR | NR |
| 43 TPN        | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| 44 TPN        | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| 45 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 14/75 | NR | 14/75 | NR | NR | NR | NR | NR | NR | NR | NR |
| 46 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 13/40 | NR | 13/40 | NR | NR | NR | NR | NR | NR | NR | NR |
| 47 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | 25/118 | NR | 25/118 | NR | NR | NR | NR | NR | NR | NR | NR |
| 48 Probiotics+EN | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| EN           | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |

(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 |
| Probiotics + EN       |        |     |     |     |       |     |        | 1/16 | 1/16 | 79.56 | 11.38 | NR  |
| EN                    |        |     |     |     |       |     |        | 10/16 | 2/16 | 39.38 | 15.31 | 15.96  |
| Prebiotics + EN       |        |     |     |     |       |     |        | 5/20 | 0/20 | NR  | NR   | NR  | 1/20 | 2/20 | 2/20 | 79.56 | 11.38 | NR  |
| Placebo + EN          |        |     |     |     |       |     |        | 25/37 | 5/37 | NR  | NR   | NR  | 2/23 | 2/23 | 15.2 | 15.2  | NR  |
| Synbiotics + EN       |        |     |     |     |       |     |        | 7/30 | 7/30 | NR  | 1/30 | 2/30 | NR  | 10/30 | 6/30 | NR  | 27.4 | 17.6 | NR  |
| EN                    |        |     |     |     |       |     |        | 10/20 | 4/20 | NR  | 3/20 | 4/20 | NR  | 10/20 | 4/20 | NR  | 24.1 | 14.2 | NR  |
| Prebiotics + EN       |        |     |     |     |       |     |        | 17/30 | 7/30 | NR  | 7/30 | NR  | NR  | 1/30 | 2/30 | NR  | 24.1 | 14.2 | NR  |
| Placebo + EN          |        |     |     |     |       |     |        | 35/35 | 5/35 | NR  | 5/35 | NR  | NR  | 3/35 | 2/35 | NR  | 28.7 | 23.4 | NR  |
| Synbiotics + EN       |        |     |     |     |       |     |        | 23/37 | 18/37 | NR  | 5/37 | 3/37 | NR  | 2/23 | 2/23 | NR  | 23.4 | 22.2 | NR  |
| EN                    |        |     |     |     |       |     |        | 8/48 | 7/48 | NR  | 4/48 | 3/48 | NR  | 3/48 | 1/48 | NR  | 14.2 | 11.6 | 8.75 |
| Prebiotics + EN       |        |     |     |     |       |     |        | 54/54 | 6/54 | NR  | 6/54 | NR  | NR  | 21.1 | 18.6 | 12.08 | 12.08| 7.125 |
| Placebo + EN          |        |     |     |     |       |     |        | 55/55 | 6/55 | NR  | 6/55 | NR  | NR  | 21.1 | 18.6 | 12.08 | 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 probiotic 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 ($p = 0.02783$), synbiotic and prebiotic therapy for diarrhea ($p = 0.01030$), probiotic therapy and EPN for diarrhea ($p = 0.01008$), 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.

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) | – |
| Probiotics | 0.71 (0.38, 1.34) | 2.90 (0.79, 11.11) | 1.60 (1.10, 2.40) | 8.30 (2.90, 25.21) |
| Prebiotics | 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.

![Rankogram and SUCRA ranking curve for nosocomial infection.](image)

**FIGURE 5** | Rankogram and SUCRA ranking curve for nosocomial infection. (A) Rankogram for nosocomial infection. A = Synbiotics, B = Probiotics, C = Prebiotics, 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.

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 favors 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 trials 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 disease 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, CRIBS, 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 |
| Probiotics     | 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, 22.96) 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 |
| 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.
| 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 | High       | –                |
| A vs. C                | Mixed estimated   | No downgrade | No downgrade | No downgrade | No downgrade   | Moderate   | Study limitations |
| A vs. D                | Mixed estimated   | No downgrade | No downgrade | Downgrade because pair heterogeneity $\chi^2$ = 68.7% | No downgrade | Low        | Inconsistency     |
| A vs. E                | Indirect estimated | No downgrade | No downgrade | No downgrade | No downgrade | Low        | Study limitations |
| B vs. C                | Mixed estimated   | No downgrade | No downgrade | No downgrade | No downgrade | High       | Inconsistency     |
| B vs. D                | Mixed estimated   | No downgrade | No downgrade | No downgrade | No downgrade   | Moderate   | Inconsistency     |
| B vs. E                | Mixed estimated   | No downgrade | No downgrade | No downgrade | No downgrade   | High       | –                |
| C vs. D                | Mixed estimated   | No downgrade | No downgrade | Downgrade because pair heterogeneity $\chi^2$ = 57.4% | No downgrade | Very low    | Study limitations |
| C vs. E                | Indirect estimated | No downgrade | No downgrade | No downgrade | No downgrade   | Moderate   | Study limitations |
| D vs. E                | Mixed estimated   | No downgrade | No downgrade | No downgrade | No downgrade   | Moderate   | Inconsistency     |
| Ranking of treatments  | Mixed estimated   | No downgrade | No downgrade | Downgrade because global heterogeneity $\chi^2$ = 62.02% | No downgrade | Low        | Study limitations |

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

The 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 in 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.

FUNDING

This study was funded by the National Natural Science Foundation of China (81971888) and the Notice of the National Health Commission medical and health science and technology development research center (2020ZX09201015).

ACKNOWLEDGMENTS

The authors would like to thank Wei Chang, Qin Sun, Fei Peng, and Shi Zhang from the department of Critical Care Medicine, Zhongda Hospital affiliated to Southeast University for their helpful and continuous support.

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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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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