Effect of gut microbiota modulation on feeding tolerance of enterally-fed critically ill adult patients: a systematic review

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Abstract

Purpose The objective of this systematic review was to evaluate the effect of pre-, pro-, and synbiotics on feeding tolerance of enterally-fed critically ill adult patients.

Methods Medline, Science Direct, Web of Knowledge, and the Cochrane Central Register of Controlled Trials were searched up to November 2019. English language randomized controlled trials reporting the effect of pre, pro or synbiotics on the feeding tolerance of enterally-fed critically ill adult patients were included.

Results Among six studies reporting the energy intake, only two studies showed significantly higher energy intake in the prebiotic-receiving groups. Among four RCTs reporting frequency or time to achieve the target calorie, only one found a significant effect of probiotics to reduce the time to achieve a target dose of calorie. About the prevalence or duration of diarrhea, 7 out of 12 RCTs reported a beneficial effect. All but one study found no beneficial effects for gut microbiota manipulation on clinical endpoints including LOS in hospital and ICU.

Conclusion It should be noticed that the heterogeneity in study designs, product format, and ICU patient populations makes it difficult to draw any general conclusion. Overall, it seems that pre, pro or synbiotics have not significant beneficial effect on feeding tolerance and clinical endpoints in critically ill adults, but they may reduce the prevalence or duration of diarrhea.

Background

Critical illness can cause hypermetabolism and hypercatabolic state that quickly depletes nutritional reserves, alters immune function and predisposes individuals to morbidities and mortality (1, 2). Critically ill patients are also likely to experience severe changes in gut function due to alterations in gut muscle contractions, secretion and absorption, gut microbiota and epithelial barrier (3-5). In this situation, early-onset and the proper amount of nutrition support are of great importance. Enteral nutrition (EN) is regarded as the favored root of nutrition support, because it protects the gut barrier, modulates immune responses and leads to a faster return of gut function. However, many critical care patients cannot receive EN due to tolerance problems (4, 6).

Enteral feeding intolerance is a common problem among critical care patients. It is often defined as either or both of the following conditions; reduced delivery of EN and presence of gastrointestinal (GI) symptoms, including diarrhea, vomiting, regurgitation, abdominal distention and high gastric residual volume (GRV) (7). Feeding intolerance often results in failure to achieve target nutritional dose as well as increased risk of pneumonia and intensive care unit (ICU) stay (8). Factors associated with feeding intolerance in critically ill patients include stress-induced hyperglycemia due to disease severity, hormonal disturbances, including high levels of cholecystokinin (CCK) and peptide YY (PYY) and low levels of motilin, administration of sedatives, analgesics, and vasopressor agents and disturbances in gut microbiota, which finally result in gastrointestinal dysfunction and manifest as feeding intolerance (9).

Gut microbiota manipulation through pre, pro or synbiotics can affect enteral feeding tolerance and energy homeostasis by altering gut muscle contractions, secretion, absorption (10-12), and regulating glucose homeostasis (13, 14), as well as affecting hormonal and immune responses, host metabolism and feeding behavior (15).

Recently, the relationship between gut microbiota and nutrition, especially in critically ill patients has been attracting considerable interest. Many studies have reported the effect of pre, pro or synbiotics on EN volume, energy intake or EN associated complication. Nevertheless, to the best of our knowledge, no systematic review or meta-analysis has been conducted to evaluate the effect of pre-, pro-, and synbiotics on feeding tolerance of enterally-fed critically ill adult patients.

Methods

This systematic review was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Additional file1) (16).

- Search strategy

A systematic search of randomized controlled trials published until November 10, 2019 was independently conducted by two authors (NS, AJE) on Medline (via PubMed), Science Direct (via Scopus and Embase), Web of Knowledge (via Web of Science) and the Cochrane Central Register of Controlled Trials (via Cochrane Library). The search strategy was designed in accordance with the database orientations using boolean operators (AND, OR), parenthesis, quotation marks and asterisks. The following search strategy was used in Medline: ("critical*" OR "critical care" OR "critical illness" OR "critically ill" OR "critically unwell" OR "severely unwell" OR "severely ill" OR "intensive care" OR "ICU" OR "CCU") AND ("tube feeding" OR "enteral*" OR "enteral feeding" OR "enteral nutrition" OR "force-feeding" OR "nasogastric*" OR "nasoduodenal*" OR "nasojejunal*") AND (prebiotic* OR probiotic* OR synbiotic* OR symbiotic) NOT (child OR pediatric OR infant OR preterm OR neonate) OR (("Enteral Nutrition" [Mesh]) AND ("Critical Care"[Mesh] OR ("tolerance" OR "intolerance" OR "tolerant" OR "intolerant") OR ("diarhea" OR "diarhoea" OR "distension" OR "distent*")) AND ("Probiotics"[Mesh] OR "Synbiotics"[Mesh] OR "Prebiotics"[Mesh])). Language restriction was applied to select articles in English. Furthermore, a manual reference check was conducted on the identified articles to find further relevant studies.

- Screening and eligibility of records

The population, intervention, comparison, outcome and study design (PICOS) strategy was used to identify inclusion criteria. The title and abstract of all identified articles were independently screened by two authors (NS, AJE). Randomized controlled trials that assessed the effect of pre, pro and synbiotics on feeding tolerance in tube-fed critically ill patients were selected. The full text of selected articles was read and assessed regarding compliance with established eligibility criteria. Discrepancies were resolved by discussion with a third researcher (RR).

Table 1 PICOS criteria for inclusion and exclusion of criteria

Abbreviations: EN, enteral nutrition; GI, gastrointestinal

- Data extraction and synthesis

The following variables were considered in data extraction: title, authors, year, country, study aim, population features (sex, age, number of participants), experimental design, intervention (the composition of prebiotic, probiotic and synbiotic, dose, and timing of administration), and main results.

- Risk of bias assessment

The five-point JADAD score was used independently by two authors (NS, AJE) to assess the quality of included studies. Discrepancies were resolved by discussion with a third researcher (MKR). The five domains of the JADAD score included being randomized, appropriately describing of randomization, being double-blind, appropriately describing blinding, and explanation of withdrawal and dropouts.

- Clinical outcomes

The clinical outcomes of interest were enteral feed volume, time to reach full enteral nutrition, the prevalence of feed intolerance and related GI complications (diarrhea, distention, high residual volume).

Results

- Study identification and selection

A total of 93 relevant articles were identified through database search and a review of reference lists of related articles. We excluded 78 articles due to the following reasons: 21 were conference abstracts or the full text was not available, 17 were not

RCTs, 13 did not exclusively enroll ICU patients, 6 were not in English, 8 did not report relevant outcomes, 5 had multiple interventions, 2 did not include exclusive EN, 1 did not have a placebo receiving control group, 5 due to other reasons. Finally, 15 RCTs, with a total of 1139 patients, were included (Figure 1). The mean JADAD score of all trials was 4.2. The minimum JADED score was 1 point for randomization. A summary of the findings of the studies is presented in Table 2.

Table 2 Randomized controlled trials evaluating the effect of pre, pro or synbiotics on feeding tolerance of enterally-fed critically ill patients

Abbreviations: NR, not reported; NGT, nasogastric tube; EN, enteral nutrition; ICU, intensive care unit; OGT, orogastric tube; GRV, gastric residual volume; VSL#3, a single daily high dose probiotic preparation.

- Effect on energy intake

Six trials examined the effect of pre, pro or synbiotics on energy intake. In one trial in 2000, 44 critically ill patients receiving EN and antibiotics were randomized to receive fiber-containing or fiber-free formula and pectin or placebo for 6 days. Mean energy intake ranged from 1200 Kcal on day 1 to 1563 Kcal on day 5. Mean energy or protein intake was not significantly different in the four study groups [18]. Rushdi et al. also evaluated the effect of guar gum enriched formula in 20 critically ill tube-fed patients with persistent diarrhea for 4 days. They showed that patients in the intervention group tolerated significantly higher formula volumes on days 1, 2 and 4. On the fourth day, the feed volume was 1775±450 ml in the intervention group compared to 1070±604 ml in the controls (p<0.01) [20]. In 2018, Fazilaty et al. evaluated the effect of EN containing β-glucan on inflammatory markers and clinical outcomes. They reported no significant difference in the mean tolerated calories between study groups (1710.5±17.03 Kcal vs. 1718.2±182.4 Kcal, p=0.6) [29]. Tuncay et al. compared the effect of an enteral formula enriched with prebiotic versus standard EN on nutritional parameters among 46 neurocritically ill patients. Results showed that feed volume and mean energy intake significantly increased from baseline to day 21 in both groups. Patients in the intervention group tolerated a significantly higher amount of energy and feed volume on day 1 and 21 [31]. Knight et al. investigated the effect of enteral synbiotic on ventilator-associated pneumonia in critically ill patients. They also reported an increase in the daily tolerated feed volume from day 1 to 7 in both groups. The feed volume ranged from 488.9± 622.8 on day 1 to 1055.6±722.6 on day 7 in the synbiotic group and from 360±431.7 to 1243.9±810.3 in the placebo group. There was no significant difference between the two groups regarding the mean tolerated enteral feed volume [21]. In another trial conducted in 2014, 40 critically ill patients were randomly assigned to receive a multi-strain probiotic or placebo for 7 days. Results showed no significant difference between groups in terms of the mean energy intake (1503.75±231.6 vs. 1617.5±185.51, p= 0.09). The percentage of patients who met energy requirements in the synbiotic and placebo groups was 84.98±3.6 and 87.24±3.92 respectively (p=0.06) [26].

Four trials assessed the effect of pre or probiotics on prevalence or time to receive the target calorie. In a trial conducted in 2001, severe sepsis or septic shock patients were randomly assigned to receive EN supplemented with partially hydrolyzed guar or fiber-free EN. All patients were on mechanical ventilation, antibiotic and catecholamine therapy. The time to reach the preconceived protein/ calorie goals was 5±3 days in prebiotic and 6±3 days in the control group. The difference was not statistically significant [19]. Malik et al. also investigated the effect of 7-days microbial cell preparation administration on the return of gut function. Time to return to normal gut function was defined as the time taken to receive a minimum of 80% of estimated calorie for a consecutive 48-hour period. They reported that patients in the treatment group achieved a faster return of gut function (3±1.75 days vs. 7±1.7 days, p<0.001) [28]. Ferrie et al. investigated the effect of *Lactobacillus rhamnosus GG* in critically ill patients with established diarrhea on feeding intolerance. The frequency of patients with feeding intolerance (tolerate less than 80% of calorie goal for 2 consecutive days) was 11.1% in the probiotic group and 16.6% in the control group (p= 0.63) [25]. Tuncay et al. also reported the prevalence of target dose achievement in 21 days intervention, as 95.7% in prebiotic supplemented and 78.3% in standard EN groups. The difference was not significant [31].

- Effect on diarrhea

In the study by Bleichner et al., 128 critically ill patients were randomized to receive *Saccharomyces*

Boulardii or placebo capsules. The prevalence of diarrhea was not significantly different between the two groups. However, treatment with *S. boulardii* reduced the mean frequency of diarrhea days per feeding days from 18.9 to 14.2% (p= 0.006) [17]. Schultz et al. investigated the effect of pectin on the prevalence of diarrhea in a critical care setting. Diarrhea was more prevalent in the placebo group compared to the intervention group (36% vs. 9%, respectively) [18]. In another trial, the mean frequency of diarrhea days was significantly lower in the fiber group. Furthermore, in the fiber group diarrhea occurred in 10.8% of feeding days, compared to 31.5% in the controls (p<0.001) [19]. Rushdi et al. also investigated the effect of soluble guar gum on the number of liquid stools during the 4 days of intervention. The number of liquid stools was significantly lower at day 4 compared to day 1 in the intervention group, while it was significantly higher in the control group. The number of liquid stools on the fourth day was 1.2±0.7 in the intervention group, compared to 2.1±0.8 in the control group (p<0.01) [20]. Knight et al. also reported the overall prevalence of diarrhea to be 5% in the synbiotic group, and 7% in the controls [21]. Another trial in 2010, examined the effect of probiotic VSL#3 on diarrhea among 45 critically ill patients. The mean frequency of diarrhea in the probiotic and placebo groups was 0.53±0.54 and 1.05±1.08 episodes per patient per day, respectively (p=0.03) [22]. Barraud et al. also investigated the effect of lactic acid bacteria on the prevalence of diarrhea. They demonstrated no significant effect of probiotic therapy on diarrhea [23]. In another RCT, Morrow et al. demonstrated that probiotic administration had no significant effect on the incidence of ICU associated diarrhea. However, the number of days with ICU-associated diarrhea was significantly higher in the probiotic group compared to the placebo group (5.9±3.8 vs. 4.1±3.7, p=0.03) [24]. Ferrie et al. also reported that critically ill patients who received probiotic had more diarrhea episodes compared to the control group, although the difference was not statistically significant [25]. Majid et al. also demonstrated that fiber-enriched EN with additional prebiotic had no significant effect on the incidence of diarrhea or length of ICU stay [27]. Shimizu et al. also investigated the effect of daily synbiotic therapy on infectious complications, including enteritis in the intensive care unit. Enteritis was defined as acute onset of continuous liquid stool for more than 12 hours. The results showed that the incidence of enteritis was significantly lower in the synbiotic group [30]. Tuncay et al. also reported that the administration of prebiotic-enriched EN was associated with a non-significant tendency toward lower rate (8.7% vs. 56.5%) and faster amelioration of diarrhea (none vs. 52.2% diarrhea on day 7) [31].

- Effect on length of stay (LOS)

The effect of pre, pro or synbiotics on ICU and hospital LOS was reported in 10 and 5 trials, respectively (Table 3). Malik et al. demonstrated that probiotic administration was associated with significantly lower ICU LOS [28]. Other studies found no significant difference between groups, regarding ICU or hospital LOS [18, 21, 22, 24, 25, 29-32].

Table 3 Reported fedding tolerance-related outcomes in RCTs evaluating the effect of pre, pro or synbiotics on feeding tolerance of enterally-fed critically ill patients

Abbreviations: NR, not reported; ICU, intensive care unit.

 Mean energy intake was reported for the entire intervention duration

Discussion

In this systematic review, 15 randomized controlled trials were reviewed to determine the potential of pre, pro or synbiotics administration to improve enteral feeding tolerance in tube-fed critically ill patients. Gut microbiota is a key regulator of gut function, host metabolism and appetite. Microbial metabolites, including SCFAs, bile acids and various neuroactives, interact with GI tract and peripheral tissue through affecting the enteric nervous system and central appetite pathways or altering bile acid signaling [33]. These effects result in changes in gastric motility and emptying [34, 35], which may reduce enteral feeding

intolerance. Besides, gut microbiota can influence intestinal barrier function and modulate the immune system, thus indirectly affect metabolism and eating behavior (15).

We found 6 studies that evaluated the effect of pre, pro or synbiotics on enteral feeding volume or energy intake. Probiotics and synbiotics had no significant effect in the majority of studies. Only 2 studies that used prebiotics (soluble guar gum for 4 days and FOS for 21 days) in the intervention group found significant beneficial effects (20, 31). Four trials evaluated the effect of pre or probiotics on frequency or time to achieve the target calorie. All studies but one found no significant effect. Microbial cell preparation administration for a consecutive 7 days was associated with a significantly faster return of gut function (28). Studies included in this review were heterogeneous in population, intervention, duration, eligibility criteria and EN protocol. To the best of our knowledge, the time to reach enteral feeding tolerance has not been studied in ICU patients. Thus, the conflicting results may be attributed to these factors. It is also believed that the beneficial effect of probiotics or synbiotics could be highly strain-specific.

In critical care setting, diarrhea is the most common gastrointestinal complication of EN (36), which may result in several unfavorable clinical conditions including enteral nutrition cessation and exacerbation of undernutrition (31). Factors that contribute to the pathogenesis of diarrhea include altered physiological responses due to EN, antibiotics administration and altered gut microbiota function (37). Therefore, gut microbiota manipulation may be an approach for the prevention and management of diarrhea in the critical care setting. For example, gut microbiota manipulation can reverse abnormal colonic water secretion by SCFAs production (38), alter colonic motor activity (39) and interfere with pathogen colonization in the gut, which protects against diarrhea (37).

Regarding the effect of probiotics on the incidence of diarrhea, 2 studies reported a trend towards reduced diarrhea incidence in the probiotic group (17, 24) and one reported a non-significant increase (23). The effect of probiotic administration on diarrhea duration was demonstrated in three of the included trials. Two of them reported a non-significant increase in diarrhea duration (24, 25), while one reported a significant decrease (17). The effect of prebiotics on the prevalence or duration of diarrhea was reported in 4 clinical trials. Two reported a significant decrease in the incidence of diarrhea (18, 19), while others reported either a non-significant increase (40) or decrease (31). Prebiotic administration was associated with a significant decrease (19) and a non-significant increase in the duration of diarrhea (40) in two studies. A non-significant decrease in the prevalence of diarrhea (21) and a significant decrease in the incidence of enteritis (30) was reported to be associated with synbiotic administration.

All but one study found no beneficial effects for gut microbiota manipulation on clinical endpoints, including LOS in hospital and ICU. A recent systematic review and meta-analysis by Manzanares et al. also showed that despite the beneficial effects of probiotic and synbiotic administration on overall infections and ventilator-associated pneumonia, these agents had no significant effect on LOS in hospital or ICU (41).

To the best of our knowledge, this systematic review was the first study to review the effect of pre, pro and synbiotics on feeding tolerance in enterally- fed critically ill patients. As we assessed relevant outcomes in a heterogeneous ICU population, our results could be attributed to a broad spectrum of critically ill patients with sepsis, trauma or other medical conditions. Although, the inclusion of diverse patient groups in this systematic review may be considered as a limitation for interpretation of the results. There was also great diversity in the type of administered prebiotic or probiotic strains, duration of treatment and dose. This heterogeneity also made it impossible to quantitively evaluate the results. Furthermore, most of the included studies reported the energy intake or feeding tolerance as a secondary outcome, not mentioning the EN protocols, while the reported EN protocols were heterogeneous in other studies.

Conclusion

Overall, the heterogeneity in studied product format, ICU patient populations, and study designs make it difficult to draw any general conclusion on the effect of pre, pro or synbiotics on feeding tolerance of critically ill tube-fed patients. We need more new well-designed trials that assess feeding tolerance as a primary endpoint and demonstrate the beneficial composition of supplements, dose, and duration to have beneficial effects.

Abbreviations

CCK: Cholecystokinin, EN: Enteral nutrition, FOS: fructo-oligosaccharide, GI: Gastrointestinal, GRV: Gastric residual volume, ICU: Intensive Care Unit, LOS: Length of stay, PICOS: population, intervention, comparison, outcome and study design, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis, PYY: Peptide YY, RCT: Randomized controlled trials, SCFAs: Short chain fatty acids

Declarations

- Ethics approval and consent to participate

Not applicable

- Consent for publication

Not applicable

- Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available, but may be available from the corresponding author on reasonable request.

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- Competing interests

No conflict of interest has been declared by the authors.

- Authors' contribution

NS: conceptualization, methodology, investigation, writing the original draft AJE: methodology, investigation, review and editing AS: review and editing, supervision MKR: methodology, formal analysis RR: conceptualization, review and editing MS: project administration, supervision.

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Tables

Table 1 PICOS criteria for inclusion and exclusion of criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Adult tube-fed critically ill patients	Partial EN
Intervention	Supplementation with pre, pro or synbiotics	
Comparison	Placebo or nothing	
Outcome	Enteral feed volume, Time to reach full enteral nutrition, the prevalence of feed intolerance and related GI complications (diarrhea, distention, high residual volume)	
Study design	Randomized controlled trials	In vitro studies

Abbreviations: EN, enteral nutrition; GI, gastrointestinal

Table 2 Randomized controlled trials evaluating the effect of pre, pro or synbiotics on feeding tolerance of enterally-fed critically ill patients

Author, Year	Population	Design	JADAD score	EN protocol	Type of intervention		
					Delivery vehicle	Intervention /dose/duration	control
Bleichner, 1997 (17)	ICU patients n=128	parallel	5	NR	NGT or jejunostomy	*EN (intact protein standard diet without fiber or lactose) + S.boulardii /500 mg four times a day/limited to 21 days or to the withdrawal of EN*	*EN (intact protein standard diet without fiber or lactose) + placebo*
Schultz, 2000 (18)	ICU patients n=44	parallel	2	NR	Tube feeding	Fiber containing formula+ pectin or fiber-free formula +pectin/ 20ml, twice daily/ 6 days	Fiber containing formula+ placebo Or fiber-free formula +placebo
Spapen, 2001(19)	ICU patients with severe sepsis or septic shock n= 25	parallel	3	Start: first 24h, 25cc/h. Increase 25-35 cc/h to 80% target	NGT	EN+ partially hydrolyzed guar/ 22g/l / a maximum of 21 days or to the withdrawal of EN	Fiber free EN
Rushdi, 2004 (20)	ICU patients with persistent diarrhea n=20	parallel	3	Start: first 18-24h. Target:25-35 kcal/kg. First day:50%, second day:75%, third day:100%	NJT	EN+ 2% soluble guar gum (Benefiber)/ 4 days	Fiber free EN
Knight, 2009 (21)	ICU patients n= 259	parallel	5	start: 30cc/h, max:80cc/h. increase or decrease according to GRV	NGT/ OGT	EN (Nutrison Energy) + Synbiotic 2000 FORTE / twice a day/ to the earliest of the following time point:28 days after admission, death or discharge	EN (Nutrison Energy) + placebo
Frohmader, 2010 (22)	ICU patients n= 45	parallel	5	Start: first 24h, 20cc/h, increase: 20cc/4h to target. Target:25-35 Kcal/kg	NGT/ OGT/ nasojejunostomy	Fiber free EN+ probiotic (VSL#3) /twice a day/ mean of 11.9 days	Fiber free EN+ placebo
Barraud, 2010 (23)	ICU patients with MV n=167	parallel	5	Starting in the first 24h, 10 Kcal/kg, increase to 30-35 Kcal/kg	NGT	EN + multi- strain probiotic (Ergyphilus)/ once a day/ until successful weaning (maximum of 28 days)	EN + placebo
Morrow, 2010 (24)	ICU patients with MV n=167	parallel	5	NR	NGT	EN + probiotic (Lactobacillus rhamnosus GG) / twice a day/	EN+ inulin-based placebo
Ferrie, 2011 (25)	ICU patients with diarrhea n= 36	parallel	5	NR	Gastric tube	Fiber containing EN+ *probiotic (*inulin-based *Lactobacillus* GG)/twice a day/ 7 days	Fiber containing EN+ placebo (inulin)
Sanaei, 2014 (26)	ICU patient n= 40	parallel	5	Start in first 24h, 25cc/h. increase 25cc/4h to target. Target:25-30 kcal/kg	NGT	Fiber containing EN+ probiotic (VSL#3)/ twice daily/ 7 days	Fiber containing EN+ placebo

Majid, 2014 [27]	ICU patients n= 22	parallel	5	Energy estimation based on Schofield equation	NGT	Fiber containing EN+ additional oligofructose/inulin/ 7g per day/ 7days	Fiber containing EN+ placebo
Malik, 2016 [28]	ICU patients n= 60	parallel	5	25 Kcal/kg. start in first 24-48h, with GRV management	NGT	EN+ multi- strain probiotic/ twice a day/ 7 days	EN+ placebo
Fazilaty, 2018 [29]	Multiple trauma ICU patients n= 40	parallel	5	Goal:25-30KCal/Kg, 75% in the 48h	NGT	EN+ prebiotic (oat β-glucan)/ 3g per day/ 21 days	EN+ placebo (maltodextrin)
Shimizu, 2018 [30]	Septic ICU patients with MV	parallel	3	Start: 20cc/h, increase: 20cc/h/day to target. Target:25-30 Kcal/kg	NGT	EN +multi- strain probiotic (Yakult BL Seichoyaku) 3 g per day+ prebiotic (galactooligosaccharides) 10g per day/ until EN stop	EN
Tuncay, 2018 [31]	Neurocritical care patients n=46	parallel	1	start:10cc/h, increase:10cc/8h till 20cc/h. reqirement:schofield equation+stress factor+activity factor+ ventilator support+fever+TEF	Nasofeeding, gastrostomy/ PEG	EN with prebiotic content/ 21 days	EN

Abbreviations: NR, not reported; NGT, nasogastric tube; EN, enteral nutrition; ICU, intensive care unit; OGT, orogastric tube; GRV, gastric residual volume; VSL#3, a single daily high dose probiotic preparation.

Table 3 Reported fedding tolerance-related outcomes in RCTs evaluating the effect of pre, pro or synbiotics on feeding tolerance of enterally-fed critically ill patients

Study	Energy intake		Achieving the target calorie		Diarrhea		Length of stay	
	intervention	control	intervention	control	intervention	control	intervention	control
Bleichner,1997 (17)	NR	NR	NR	NR	Prevalence: 18/64 (24%) days w/ diarrhea per feeding days: 14.2%	Prevalence: 24/64 (38%) days w/ diarrhea per feeding days: 18.9%	NR	NR
Schultz, 2000 (18)	Mean⏰	Mean⏰	NR	NR	Prevalence: 1/11 (9%)	Prevalence: 4/11 (36%)	Hospital: 34±14.7 ICU: 28±14.6	Hospital: 24.4±9 ICU: 17.2±8.2
Spapen, 2001 (19)	NR	NR	Time to: 5±3 days	Time to: 6±3days	Prevalence: 6/13 (46%) Days w diarrhea per feeding days: 16/148(10.8%)	Prevalence: 11/12(92%) Days w diarrhea per feeding days: 46/146(31.5%)	NR	NR
Rushdi, 2004 (20)	Day 1-4	Day 1-4	NR	NR	Liquid stools day1-4	Liquid stools day1-4	NR	NR
Knight,2009 (21)	Day1-7	Day1-7	NR	NR	Prevalence: 7/130 (5%)	Prevalence: 9/129(7%)	ICU: 6 (3-11)	ICU: 7 (3-14)
Frohmder,2010 (22)	NR	NR	NR	NR	Frequency of liquid stools: 0.53±0.54	Frequency of liquid stools: 1.05±1.08	ICU: 7.3±5.7	ICU: 8.1±4
Barraud, 2010 (23)	NR	NR	NR	NR	Prevalence: 48/87(55.2)	Prevalence: 42/80(52.5)	Hospital: 26.6±22.3 ICU: 18.7±12.3	Hospital: 28.9±26.4 ICU: 20.2±20.8
Morrow, 2010 (24)	NR	NR	NR	NR	Prevalence: 44/70(62.9) Days w/ diarrhea: 5.9±3.8	Prevalence: 42/68(61.8) Days w/ diarrhea: 4.1±3.7	Hospital: 21.4±14.9 ICU: 14.8±11.8	Hospital: 21.7±17.4 ICU: 14.6±11.6
Ferrie, 2011 (25)	NR	NR	Prevalence 16/18(88.8)	Prevalence 15/18(83.33)	Diarrhea duration: 7.22±3.63 Loose stool per day: 3.14±1.23	Diarrhea duration: 5.72±2.88 Loose stool per day: 3±1.2	Hospital: 54.5±31.26 ICU: 32.04±24.46	Hospital: 59.04±33.92 ICU: 29.75±18.81
Sanaei, 2014 (26)	Mean⏰	Mean⏰	NR	NR	NR	NR	NR	NR
Majid,2014 (27)	NR	NR	NR	NR	Prevalence: 11/12(92) Days w/ diarrhea: 3.9±4.1	Prevalence: 9/10(90) Days w/ diarrhea: 3.8±3.5	NR	NR
Malik, 2016 (28)	NR	NR	Time to: 3±1.75 days	Time to: 7±1.7 days	NR	NR	ICU: 10.9±3.9	ICU: 15.8±7.8
Fazilaty,2018 (29)	Mean⏰	Mean⏰	NR	NR	NR	NR	ICU: 27.55±7.8	ICU: 31.2±15.8
Shimizu,2018 (30)	NR	NR	NR	NR	Incidence of enteritis: 2/35 (6.3)	Incidence of enteritis: 10/37(27)	ICU: 23 (13-43)	ICU: 28 (17-45)
Tuncay,2018 (31)	Day 1 and 21	Day 1 and 21	Prevalence 22 (95.7)	Prevalence 18 (78.3)	Prevalence: 8.7%	Prevalence: 56.5%	Hospital stay<40	Hospital stay<40

											days: 56.6%	days: 60.9%
											Hospital stay>=41 days: 43.4%	Hospital stay>=41 days: 39.1%
											ICU stay<40 days: 69.5%	ICU stay<40 days: 69.5%
											ICU stay>=41 days: 43.5%	ICU stay>=41 days: 30.4%

Abbreviations: NR, not reported; ICU, intensive care unit.

⸎ Mean energy intake was reported for the entire intervention duration

Figures
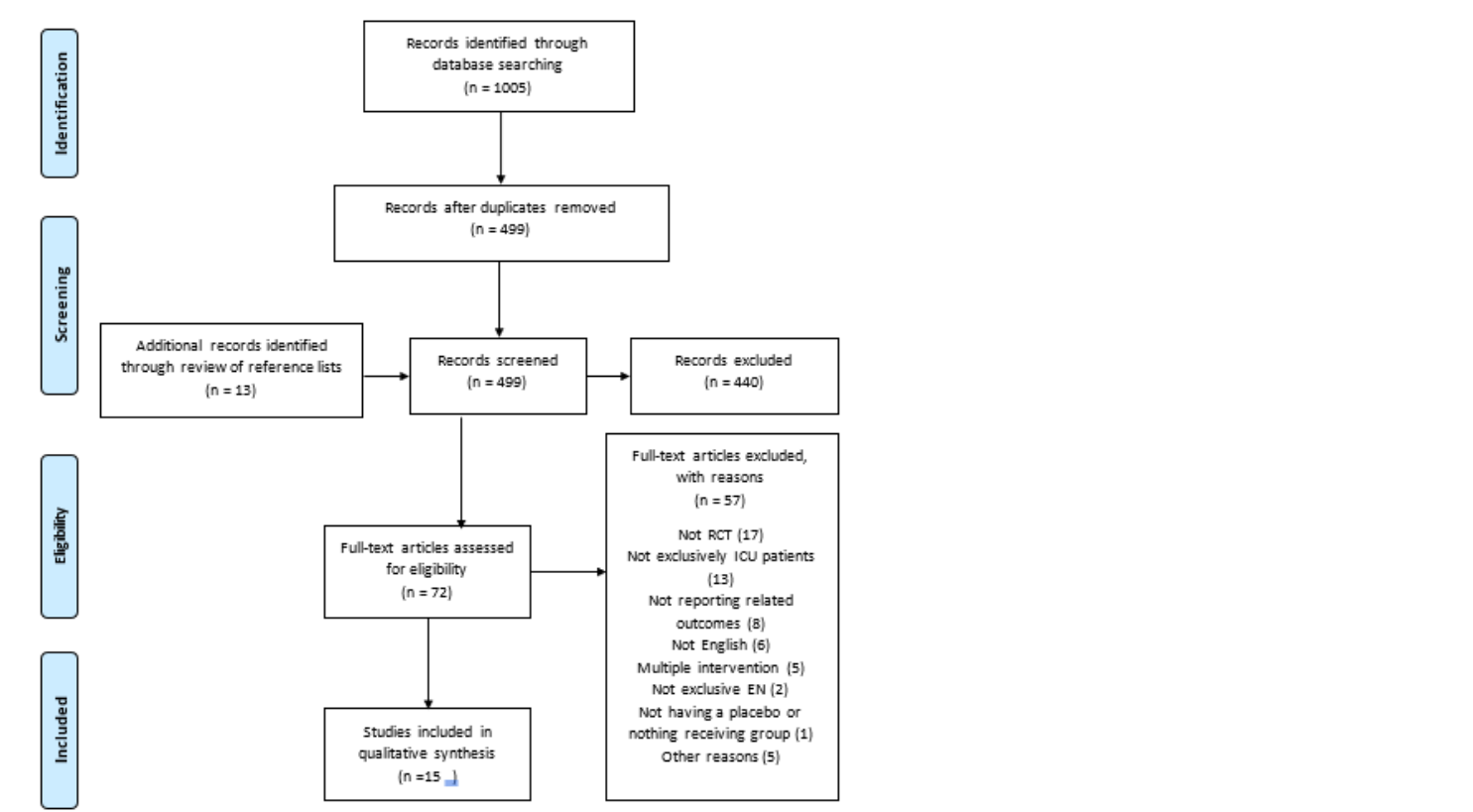
Figure 1

Flow diagram of the literature search process