Literature Review

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Glycemic and gastrointestinal outcomes of intermittent or sequential versus continuous enteral nutrition in critically ill adults: a systematic review

Luaran glikemik dan gastrointestinal nutrisi enteral intermiten atau sekuensial dibandingkan kontinu pada pasien dewasa sakit kritis: tinjauan sistematis

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Luh Marina Wirahartari[1*], Christian[2]

Abstract

Background: The metabolic effects of different enteral feeding schedules remain uncertain despite previous evidence synthesis.
Objectives: To examine the glycemic and gastrointestinal outcomes of intermittent or sequential versus continuous enteral nutrition in critically ill adults.
Methods: PubMed, Europe PMC, and Epistemonikos were searched up to September 18, 2026. Randomized controlled trials reporting at least one glycemic outcome were eligible. Two reviewers independently selected studies, extracted data, and assessed risk of bias. Findings were synthesized narratively by feeding regimen and outcome. The review was not prospectively registered, and evidence certainty was not formally graded.
Results: Four trials included 295 participants. Glycemic findings varied across regimens; lower insulin requirements did not consistently accompany lower glucose variability. Gastrointestinal findings differed by outcome definition and observation period. Nutritional outcomes were incompletely comparable across studies. A mortality difference in one small trial was accompanied by baseline illness-severity imbalance and few events, limiting causal interpretation.
Conclusions: The available trials are insufficient to establish a superior feeding regimen or equivalent effectiveness and safety. The interpretation should account for the protocol differences, risk of bias, and imprecision. Larger trials using standardized outcomes are required.

Keywords:
Blood glucose, critical illness, enteral nutrition, gastrointestinal symptoms, insulin

Abstrak

Latar Belakang: Efek metabolik berbagai jadwal pemberian nutrisi enteral masih belum pasti meskipun telah tersedia sejumlah sintesis bukti.
Tujuan: Mengkaji luaran glikemik dan gastrointestinal nutrisi enteral intermiten atau sekuensial dibandingkan kontinu pada pasien dewasa sakit kritis.
Metode: PubMed, Europe PMC, dan Epistemonikos ditelusuri hingga 18 September 2026. Uji acak terkontrol yang melaporkan sedikitnya satu luaran glikemik memenuhi syarat inklusi. Dua penelaah secara independen menyeleksi studi, mengekstraksi data, dan menilai risiko bias. Temuan disintesis secara naratif menurut regimen pemberian nutrisi dan luaran. Tinjauan ini tidak diregistrasikan secara prospektif, dan kepastian bukti tidak dinilai secara formal.
Hasil: Empat uji mencakup 295 peserta yang dianalisis. Temuan glikemik bervariasi antarregimen: kebutuhan insulin yang lebih rendah tidak selalu disertai variabilitas glukosa yang lebih rendah. Temuan gastrointestinal berbeda

[1] Clinical Nutrition Department, Klungkung Regional General Hospital, Bali, Indonesia.E-mail: marinawira@gmail.com
[2] Clinical Nutrition Department, Klungkung Regional General Hospital, Bali, Indonesia. E-mail: christianadiutamasugiarto@gmail.com

Corresponding Author:
Wirahartari Luh Marina: Clinical Nutrition Department, Klungkung Regional General Hospital, Bali, Indonesia. E-mail: marinawira@gmail.com
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menurut definisi luaran dan periode pengamatan. Luaran nutrisi tidak sepenuhnya dapat dibandingkan antarstudi. Perbedaan mortalitas pada satu uji kecil disertai ketidakseimbangan keparahan penyakit awal dan sedikit kejadian, sehingga membatasi interpretasi kausal.
Kesimpulan: Bukti yang tersedia belum cukup untuk menetapkan regimen yang unggul maupun kesetaraan efektivitas dan keamanan. Interpretasi perlu mempertimbangkan perbedaan protokol, risiko bias, dan ketidakpresisian. Diperlukan uji yang lebih besar dengan luaran terstandar.

Kata Kunci:
Gejala gastrointestinal, glukosa darah, insulin, nutrisi enteral, sakit kritis

Introduction

Enteral nutrition (EN) is a cornerstone of nutritional support for critically ill patients admitted to the intensive care unit (ICU), given its recognized advantages of preserving gastrointestinal integrity, modulating immune function, and reducing infectious complications compared with parenteral nutrition (Heffernan et al., 2022; Hu et al., 2025). Among the many clinical decisions surrounding EN delivery, the choice between continuous enteral nutrition (CEN) and intermittent enteral nutrition (IEN) remains a persistent point of clinical uncertainty. While gastrointestinal tolerance outcomes, such as diarrhea, constipation, and gastric residual volume, have received considerable attention in the literature, glycemic variability and insulin requirements represent an important and comparatively underexplored dimension of this debate, given their established association with adverse outcomes in critically ill populations (Zhang et al., 2026).

Historically, continuous feeding has been the preferred default strategy in ICUs, largely because it is believed to provide steady nutrient delivery and more stable serum glucose concentrations, thereby minimizing large postprandial glycemic excursions (Heffernan et al., 2022; Wu et al., 2023). ESPEN recommends continuous rather than bolus enteral nutrition in critically ill patients, whereas ASPEN/SCCM suggests continuous infusion for patients at high risk of aspiration or with intolerance to bolus gastric feeding (McClave et al., 2016; Singer et al., 2023). Conversely, intermittent feeding has been proposed as more physiologically aligned with natural circadian and hormonal rhythms, potentially promoting pulsatile secretion of gastrointestinal hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which may influence glucose homeostasis differently than continuous infusion (Wang et al., 2026). Several individual RCTs have attempted to characterize these metabolic effects; McNelly et al. (2020), as summarized in Heffernan et al. (2022), reported no episodes of hypoglycemia in either feeding arm but a numerically higher incidence of hyperglycemia with intermittent feeding (50%) compared with continuous feeding (33.3%), whereas Shahriari et al. (2015) found no statistically significant difference in mean blood glucose concentrations between groups.

Several systematic reviews and meta-analyses have compared intermittent and continuous enteral nutrition, including those by Heffernan et al. (2022), Abdelbaky et al. (2024), Hu et al. (2025), Panwar et al. (2025), Wang et al. (2026), and Zhang et al. (2026). The present review addresses a narrower question: how do glycemic variability and exogenous insulin requirements differ across specific feeding schedules, and how should these findings be interpreted in conjunction with gastrointestinal outcomes? Mean glucose levels alone may obscure differences in glucose excursions or insulin exposure. The contribution of this review is a regimen-specific appraisal of these distinct outcomes rather than a comprehensive update of all comparative safety evidences. Its restriction to recent trials reporting glycemic outcomes also limits the breadth of this contribution.

This systematic review aimed to synthesize randomized controlled trials comparing intermittent or sequential with continuous gastric enteral nutrition in critically ill adults, with glycemic variability as the primary review outcome. Secondary outcomes were mean and peak glucose, hypoglycemic and hyperglycemic events, exogenous insulin requirements, gastrointestinal tolerance, nutritional delivery and target attainment, feeding interruptions, ICU and hospital length of stay, mortality, aspiration, and other feeding-related adverse events.

For this synthesis, intermittent feeding is an umbrella term for schedules with discrete feeding

sessions or planned feeding-free periods and does not imply physiological equivalence. Regimens are distinguished as discrete bolus-like or intermittent infusions, diurnal feeding with overnight fasting, daytime feeding with a nocturnal pause, and sequential feeding after initial continuous nutrition. Sequential feeding was retained because it compares a transition to scheduled feeding with continued continuous feeding; however, its effects apply to patients who have already tolerated initial nutrition. The results were interpreted within each regimen rather than as a uniform intermittent feeding effect.

Methods

This systematic review was reported in reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. It was not prospectively registered. The PRISMA guides reporting and does not, by itself, establish methodological quality. The absence of prospective registration limits the independent assessment of whether eligibility criteria, outcome priorities, and synthesis decisions preceded knowledge of the findings.

Literature Search

Two reviewers independently searched PubMed, Europe PMC, and Epistemonikos for records available until September 18, 2026. Searches were restricted to English-language publications from the preceding five years, and a full-text availability filter was applied in Europe PMC. Trial registries and reference lists were not systematically searched for. The search expression was: (("Enteral Nutrition" OR "enteral feeding" OR "tube feeding") AND ("intermittent" OR "bolus" OR "cyclic" OR "diurnal") AND ("continuous" OR "continuous infusion") AND ("Intensive Care Units" OR "critically ill" OR "ICU")) AND ("randomized controlled trial"[pt] OR "randomized" OR "RCT"). The [pt] field tag applies to PubMed and should not be interpreted as syntax for other databases.

Eligibility Criteria

Two reviewers independently assessed eligibility during the title and abstract screening and full-text review. Disagreements were resolved through discussion and consensus-building.

Studies were eligible if they met the following PICOS criteria: (1) Population: critically ill adults aged ≥18 years admitted to an ICU and receiving nasogastric or orogastric enteral nutrition for ≥48 h; (2) Intervention: intermittent gastric feeding, including bolus-like, diurnal, or nocturnal-pause regimens, or a sequential transition from continuous to intermittent feeding; (3) Comparator: continuous gastric enteral nutrition delivered over 18–24 hours/day; (4) Outcomes: at least one glycemic outcome, including variability, serial glucose measurements, mean or peak glucose, hypoglycemia, hyperglycemia, or exogenous insulin requirements; and (5) Study design: full-text randomized controlled trials reporting outcome data.

Glycemic variability was the primary review outcome, whereas reporting any eligible glycemic outcome was sufficient for study inclusion. This distinction allowed the inclusion of trials reporting dysglycemic events without a continuous variability measure, but these trials could not directly inform the primary outcome. Variability measures, including daily glucose range (maximum minus minimum), glucose standard deviation, and coefficient of variation, were considered separately from mean or peak glucose and serial time-point comparisons. The coefficient of variation expresses glucose standard deviation relative to the mean as a percentage. Study-specific measurement methods and time windows were retained. Secondary outcomes comprised the other glycemic outcomes, gastrointestinal tolerance, nutritional delivery and target attainment, feeding interruptions, and clinical and safety outcomes.

Studies were excluded for exclusively pediatric/neonatal populations, total parenteral nutrition, exclusively post-pyloric/jejunal feeding, feeding interventions lasting <48 h, ineligible designs (observational studies, reviews, case reports, or protocols without outcome data), conference abstracts lacking complete quantitative data, and absence of an eligible glycemic outcome.

Excluding exclusively post-pyloric feeding restricted the review to gastric delivery and gastric tolerance outcomes. The ≥48-hour threshold allowed observation across at least two daily feeding cycles and was a scope decision rather than a validated clinical cutoff. Requiring a glycemic outcome focused the review on metabolic effects but could exclude trials informative about gastrointestinal or clinical safety. Consequently, the secondary-outcome synthesis represents the eligible glycemic-reporting trials rather than all evidence on enteral-feeding safety. The language, publication period, and full-text restrictions may also have reduced retrieval.

Study Selection and Identification

Two reviewers independently screened titles and abstracts using Rayyan, followed by full-text

assessment of potentially eligible studies. The systematic search identified 191 records from database searching, with no additional records identified through registers. Following the removal of 29 duplicate records, 162 unique records remained for title and abstract screening. Of these, 150 records were excluded as they did not meet the predefined eligibility criteria, leaving 12 reports for full-text retrieval, all of which were successfully obtained.

These 12 reports were assessed in full for eligibility, resulting in the exclusion of eight studies: five were excluded due to incorrect outcome measures and three due to incorrect intervention. Ultimately, four studies satisfied all inclusion criteria and were included in the narrative synthesis, corresponding to four reports of the included studies. The complete study selection process, including reasons for exclusion at each stage, is presented in the PRISMA flow diagram (Figure 1).

Data Collection Process and Data Items

Two reviewers independently extracted data using a standardized form. The extracted items included study identity, country, sample size, age, sex, illness severity, feeding schedule and duration, and glycemic, gastrointestinal, nutritional, and clinical outcomes.

In this synthesis, randomized and analyzed populations are distinguished where reported, and outcome-specific denominators and observation windows are retained. Insulin-treated patient counts, administration frequency, cumulative exogenous insulin dose, and plasma insulin concentrations are treated as different measures. Ambiguous reporting is not interpreted as evidence that an outcome was absent.

Risk of Bias Assessment

Two reviewers assessed the risk of bias using the Cochrane RoB 2 framework, considering the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Disagreements were resolved by discussion and consensus. Table 1 summarizes the study-level judgments reported for this review. Because RoB 2 judgments concern a specific result, this summary cannot be assumed to apply to every outcome or time point. Therefore, the interpretation also considers the outcome-specific concerns described in the Results and Discussion; the table alone does not establish a complete result-level assessment.

The certainty of evidence was not formally assessed using GRADE. Risk-of-bias judgments for individual studies do not substitute for an outcome-level assessment of certainty across studies. Accordingly, the synthesis provides no graded recommendation for a preferred feeding regimen, and nonsignificant results are not interpreted as evidence of equivalence.

Data Synthesis

The results were organized by outcome domain and feeding regimen, retaining the trial-specific observation period and summary statistics. Quantitative pooling was not performed. For glycemic variability, studies used different indices or serial glucose comparisons, and insulin outcomes represented patient counts, treatment frequency, or cumulative dose.

Gastrointestinal definitions and observation windows differed, and nutritional target attainment was not consistently a post-randomization outcome. Clinical events were sparse and follow-up was not uniform. These differences limited the clinical interpretability of the common pooled estimate. The narrative synthesis describes the findings and their limitations without counting statistically significant results as votes for superiority.

Table 1. Study-level summary of reported RoB 2 judgments

Study	D1	D2	D3	D4	D5	Overall
Beattie et al., 2025	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns
Goksu et al., 2025	Some concerns	Some concerns	High	Low	Some concerns	High risk
Saiz-Vinuesa et al., 2025	Low	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Yao et al., 2025	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns

D1, randomization process; D2, deviations from the intended interventions; D3, missing outcome data; D4, outcome measurement; D5, selection of the reported result. These summary judgments are not interchangeable across outcomes or time points and require result-specific supporting evidence.

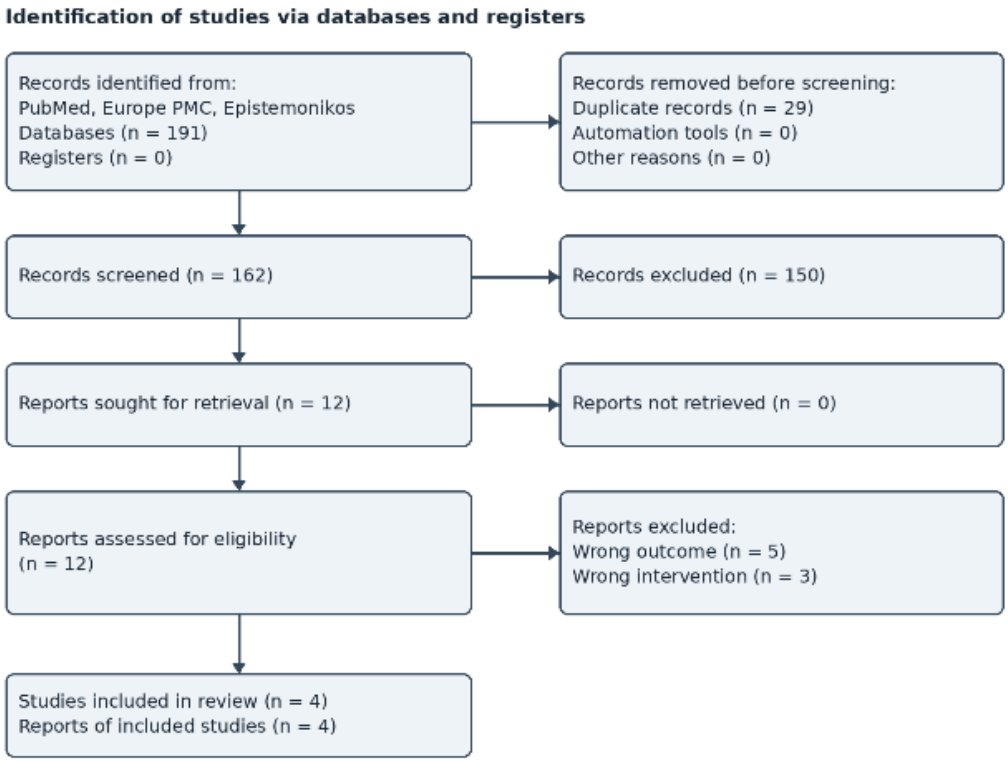


Figure 1. PRISMA 2020 study selection flow diagram

Results

Characteristics of Included Studies

Four randomized controlled trials published in 2025 contributed 295 analyzed participants from ICUs in the United Kingdom, Turkey, Spain, and China (Table 2). The analyzed samples were 28 in Beattie et al., 93 in Goksu and Tuncel, 40 in Saiz-Vinuesa et al., and 134 in Yao et al. The total number of 295 should not be interpreted as the total randomized population. Beattie et al. randomized 30 participants (13 intermittent and 17 continuous); one intermittent participant required jejunal feeding and one withdrew consent, leaving 28 analyzed. Yao et al. reported 158 randomized participants but analyzed 65 in the sequential group and 69 in the continuous group, a difference of 24 participants (15.2%). Although the publication describes its analysis as intention-to-treat, this discrepancy requires consideration when interpreting attrition and precision.

The populations differed in terms of illness severity, diagnoses, and diabetes eligibility. In the study by Saiz-Vinuesa et al. (2025), baseline APACHE II scores were higher in the continuous group than in the intermittent group (21.22 ± 5.57 vs. 16.91 ± 5.40; p = 0.018), indicating greater initial illness severity in the group with higher observed mortality. Goksu and Tuncel (2025) and Yao et al. (2025) excluded diabetes, whereas Saiz-Vinuesa et al. excluded insulin-dependent diabetes and included seven participants with non-insulin-dependent type 2 diabetes. Beattie et al. included two participants with type 2 diabetes, both in the continuous arm. These differences limit direct comparisons of glycemic findings across trials.

The feeding protocols and observation periods also differed (Table 2). Beattie et al. evaluated three daily feeds infused over 30–60 min with overnight fasting during a 48-hour intervention. Goksu and Tuncel compared four daily 40-min bolus feeds, daytime infusion cycles with a six-h nocturnal pause, and feeding continued overnight for seven days. Saiz-Vinuesa et al. used four one-h infusions at six-h intervals, with follow-up during enteral feeding for up to 15 days. In Yao et al., all participants initially received continuous feeding and achieved ≥80% of their energy target before randomization. The sequential arm then received three 2-h feeding periods (07:00–09:00, 11:00–13:00, and 17:00–

19:00), with outcomes assessed seven days after randomization. This trial therefore evaluated a transition strategy among patients already tolerating nutrition.

Feeding schedules, formula composition, and follow-up durations varied across trials. Energy targets were estimated using the Harris–Benedict equation in Goksu and Tuncel (2025) and Saiz-Vinuesa et al. (2025), whereas Yao et al. (2025) used a weight-based target of 25–30 kcal/kg/day. These differences, together with variations in prescribed and delivered nutrient doses, limit direct comparability of nutritional exposure across studies.

Glycemic Parameters and Insulin Requirements

Glycemic outcomes are summarized in Table 3. In Beattie et al. (2025), the highest recorded glucose did not differ significantly on day 1 (9.7 vs. 8.4 mmol/L; p = 0.053) or day 2 (9.4 vs. 9.1 mmol/L; p = 0.980). These values describe daily maxima, not mean glucose. The daily range, defined as the highest minus lowest recorded glucose, was greater with intermittent feeding on day 1 (2.7 vs. 1.5 mmol/L; p = 0.017), but not on day 2 (p = 0.767). Higher peak plasma insulin concentrations should be distinguished from exogenous insulin treatment. In Goksu and Tuncel (2025), glucose was measured four times daily for seven days. Serial glucose comparisons suggested differing temporal patterns, but these analyses do not provide a directly comparable patient-level variability index. The proportions receiving insulin were 5/31, 11/31, and 15/31 in the nocturnal-pause, bolus, and continuous groups, respectively (overall three-group p = 0.025). This omnibus test does not establish a specific pairwise effect. The separately reported frequency of insulin requirements among treated patients also differed from cumulative dose and was not statistically significant across groups (p = 0.177). Beattie's exploratory 10:00 glucose difference on day 2 did not remain significant after correction for multiple comparisons and should not be presented as a confirmed treatment effect.

Table 2. Characteristics of the included randomized trials

Study; country	Population and analysis denominator	Feeding protocol	Nutritional target	Duration
Beattie et al. (2025); UK	Adults requiring gastric EN >48 h; randomized IEN/CEN: 13/17; analyzed: 11/17. Two IEN exclusions.	IEN: three sessions/day, 30–60 min/session, with overnight fasting (19:00–08:00); CEN: 24-h infusion.	Day 1:600 mL/day; Day 2: calculated daily energy requirement.	48 h
Goksu & Tuncel (2025); Turkey	Intubated patients with sepsis; diabetes excluded; IF/BF/CF: 31/31/31	IF: daytime infusion cycles, 06:00–24:00, with a six-hour overnight pause. BF: four 40-min sessions/day. CF: continued feeding overnight.	Harris–Benedict energy target; protein ≥1.2 g/kg/day. Time to target defined as reaching 75% of calculated energy.	7 days
Saiz-Vinuesa et al. (2025); Spain	Adult ICU patients starting NG feeding within 48 h; IEN/CEN: 22/18	IEN: four sessions/day, 1 h/session, every 6 h. CEN: 24-h infusion.	Harris–Benedict estimate with stress factor, or 20–25 kcal/kg/d.	Up to 15 days
Yao et al. (2025); China	Adults tolerating ≥80% of the energy target before randomization; 158 randomized, 134 analyzed (SF/CF: 65/69); diabetes was excluded.	After initial continuous feeding and randomization, SF was administered three 2-h sessions/day, and CF was continued.	25–30 kcal/kg/day.	7 days after randomization

All trials were single-center RCTs. NG, nasogastric; IEN/IF, intermittent enteral feeding; CEN/CF, continuous enteral feeding; BF, bolus feeding; SF, sequential feeding. The denominators are analyzed samples unless specified. Beattie et al. excluded two of 13 intermittent-arm participants after randomization (jejunal feeding and consent withdrawal); all 17 continuous-arm participants were analyzed. For Yao et al., 24 of 158 randomized participants were not represented in the reported analysis set. In Saiz-Vinuesa et al., baseline APACHE II differed (IEN: 16.91 ± 5.40; CEN: 21.22 ± 5.57; p = 0.018).

Table 3. Key glycemic outcomes and insulin requirements

Study	Outcome	Intermittent /sequential	Continuous	Bolus	p-value
Beattie et al. (2025)	Daily glucose range (maximum−minimum), day 1, mmol/L	2.7 (2.3–4.7)	1.5 (1.0–2.7)	—	0.017
	Daily glucose range (maximum−minimum), day 2, mmol/L	2.2 (1.4–3.8)	2.2 (1.8–3.3)	—	0.767
	Glucose at 10:00 on day 2, mmol/L; exploratory time point	10.6 ± 2.5	8.4 ± 2.4	—	0.040; unadjusted
	Patients receiving insulin, n/N	01-Nov	0/17	—	0.393
Goksu & Tuncel (2025)	Serial glucose profile: four measurements/day for 7 days	See text	See text	See text	Multiple time-point tests; see text
	Hyperglycemia >180 mg/dL requiring insulin, n/N	May-31	15/31	Nov-31	0.025; three groups
	Hypoglycemia <70 mg/dL, n/N	Apr-31	Feb-31	Feb-31	0.579; three groups
Saiz-Vinuesa et al. (2025)	Hypoglycemia <70 mg/dL, n/N	Apr-22	Feb-18	—	0.53
	Hyperglycemia >300 mg/dL, n/N	Feb-22	Mar-18	—	0.47
Yao et al. (2025)	Mean glucose over 7 days, mmol/L	8.8 (7.8–10.8)	9.5 (7.9–11.1)	—	0.391
	Glucose coefficient of variation, %	11.9 (8.7–16.1)	7.9 (5.6–11.1)	—	<0.001
	Patients receiving insulin, n/N	27/65	37/69	—	0.162
	Cumulative insulin dose over 7 days, U	0 (0–59)	28 (0–213)	—	0.035

Values are presented as mean ± SD, median (IQR), or n/N, as displayed. Rows containing a bolus arm report overall three-group p-values, not an intermittent-versus-continuous pairwise test. Other p-values compare the two displayed groups. Serial time-point analyses in Goksu and Tuncel are not a patient-level SD or coefficient of variation; qualitative rankings have therefore been removed. Measurement periods and glucose thresholds differ across studies. In Beattie et al., the day-2 10:00 glucose comparison was not significant after correction for multiple comparisons. The daily-range rows had one missing continuous-arm measurement; day-2 maxima exclude the intensive sampling period.

Table 4. Key nutritional, gastrointestinal, and clinical outcomes

Study	Outcome	Intermittent /sequential	Continuous	Bolus	p-value
Beattie et al. (2025)	Nutrition delivered as % of target, day 2, median (IQR)	100 (100–100)	105 (92–110)	—	0.43
	Diarrhea during 48 h, n/N (%)	5/11 (45.5%)	0/17 (0%)	—	0.005
	Delayed gastric emptying during 48 h, n/N	01-Nov	Mar-17	—	0.635
	Vomiting during 48 h, n/N	0/11	Feb-17	—	0.505
	ICU mortality, n/N	01-Nov	Feb-17	—	—
Goksu & Tuncel (2025)	Time to 75% of energy target, days	2.33 ± 0.48	2.52 ± 0.51	2.45 ± 0.62	0.414; three groups
	High GRV during 7 days, n/N	Jun-31	Jul-31	Dec-31	0.183; three groups
Saiz-Vinuesa et al. (2025)	Energy target achieved, n/N	17/22	16/18	—	0.33
	Time to energy target, h, median	34	36	—	0.28
	Diarrhea during EN follow-up, n/N	May-22	Mar-18	—	0.63
	Vomiting, n/N	Apr-22	Apr-18	—	0.75
	Feeding interruptions, median	1	2.5	—	<0.010
	ICU stay, days, median	23	12.5	—	0.72

Study	Outcome	Intermittent /sequential	Continuous	Bolus	p-value
	Mortality during EN follow-up (≤15 days), n/N	Jan-22	May-18	—	0.04
Yao et al. (2025)	GRV ≥250 mL, n/N	Feb-65	Apr-69	—	>0.05
	Diarrhea frequency	Similar between groups	Similar between groups	—	>0.05
	ICU stay, days, median	24	22	—	0.848
	Hospital mortality, n/N	Jun-65	Sep-69	—	0.484

GRV, gastric residual volume; NR, not reported. For Goksu and Tuncel, p-values are overall three-group tests; high GRV was defined as >250 mL in the Methods (≥250 mL in the abstract). Definitions and follow-up vary across studies. A dash in the p-value column indicates that no inferential p-value is presented; it should not be interpreted as evidence of no difference. In Yao et al., achieving ≥80% of the energy target was a prerequisite for randomization, not a comparative nutritional outcome.

Yao et al. (2025) reported no statistically significant difference in mean seven-day glucose (8.8 vs. 9.5 mmol/L; p = 0.391), but greater variability with sequential feeding: coefficient of variation, 11.9% vs. 7.9% (p < 0.001), and SD, 1.1 vs. 0.8 mmol/L (p = 0.002), respectively. The cumulative seven-day insulin dose was lower in the metformin group (median 0 vs. 28 U; p = 0.035), whereas the proportion of patients receiving insulin was not significantly different (27/65 vs. 37/69; p = 0.162).

Saiz-Vinuesa et al. (2025) reported dysglycemic events rather than a continuous variability measure: hypoglycemia occurred in 4/22 versus 2/18 participants and hyperglycemia in 2/22 versus 3/18, without statistically significant differences. Thus, glucose variability, mean glucose levels, and exogenous insulin exposure did not show a uniform pattern. Differences in trial populations, regimens, measurement methods, and time windows preclude the attribution of these patterns to feeding periodicity alone.

Nutritional Achievement

Nutritional outcomes were not uniformly measured (Table 4). Beattie et al. (2025) reported a median day-2 delivery of 100% (IQR 100–100) and 105% (92–110) of the target in the intermittent and continuous groups, respectively (p = 0.430), without a statistically significant difference in delivered kilocalories. Goksu and Tuncel (2025) defined target attainment as reaching 75% of the calculated energy requirements; the time to reach this threshold did not differ significantly among the three groups (overall p = 0.414). Their reported values of 1695, 1664, and 1599 kcal were calculated targets, not evidence of equivalent delivered intakes.

Saiz-Vinuesa et al. (2025) reported target attainment in 17/22 intermittent and 16/18 continuous-feeding participants (p = 0.33). In Yao et al. (2025), achieving ≥80% of the target preceded randomization and could not demonstrate an effect of the allocated regimen. These findings do not establish equivalent nutritional adequacy or exclude clinically important differences in delivered energy or protein.

Feeding Intolerance

Gastrointestinal outcomes were assessed using different definitions and observation periods. Unless otherwise stated, the values below are presented as intermittent versus continuous feeding.

During the 48-hour intervention, Beattie et al. (2025) defined diarrhea as Bristol Stool Chart type 6 or 7 stools or more than three stools within 24 hours, and delayed gastric emptying as gastric residual volume (GRV) >250 mL on two occasions within 24 hours. Diarrhea occurred more frequently with intermittent feeding (45.5% vs. 0%, p = 0.005) than with continuous feeding. No statistically significant differences were observed in delayed gastric emptying (9.1% vs. 17.6%, p = 0.635) or vomiting (0% vs. 11.8%, p = 0.505), and neither group experienced aspiration or ileus.

Goksu and Tuncel (2025) distinguished the proportion of patients experiencing high GRV from the reported mean frequency of such events. High GRV occurred in 6/31, 12/31, and 7/31 patients receiving nocturnal-pause, bolus, and continuous feeding, respectively (overall p = 0.183). The reported mean HGRV rates were 1.17 ± 0.41, 2.08 ± 0.67, and 1.71 ± 0.49 (overall p = 0.014). The publication reported a bolus-versus-nocturnal-pause difference; however, the omnibus result

should not be used to infer a nocturnal-pause-versus-continuous benefit. Frequency, patient incidence, and residual volume in milliliters are distinct outcomes.

Saiz-Vinuesa et al. (2025) assessed complications during enteral feeding, with follow-up ending at discontinuation or change of the assigned regimen, transfer, death, or a maximum of 15 days. Elevated GRV was defined as >500 mL, while diarrhea was defined by liquid stools, at least five daily bowel movements, or estimated stool volume >2,000 mL/24 hours. No statistically significant differences were observed in vomiting (18.2% vs. 22.2%, p = 0.75), diarrhea (22.7% vs. 16.7%, p = 0.63), or elevated GRV (4.5% vs. 0%, p = 0.36). Intermittent feeding was associated with fewer feeding interruptions (median 1 vs. 2.5, p = 0.005).

Yao et al. (2025) recorded gastric retention, defined as gastric volume ≥250 mL, and defecation and diarrhea episodes over 7 days after randomization. Gastric retention occurred in 3.1% of the sequential-feeding participants and 5.8% of the continuous-feeding participants. No statistically significant differences were reported in gastric retention, defecation, or diarrhea episode counts (all p > 0.05). An operational definition of diarrhea was not identified in the available main report.

Overall, the gastrointestinal findings were inconsistent across the trials. Differences in outcome definitions, feeding regimens, and observation periods limit direct comparisons and do not establish that a particular protocol characteristic explains the observed effects of EN.

Clinical Outcomes and Safety

Clinical outcomes were sparse and were measured over different periods (Table 4). Beattie et al. reported ICU deaths in 1/11 intermittent and 2/17 continuous feeding participants. ICU and hospital length of stay did not differ significantly. In Saiz-Vinuesa et al. (2025), deaths occurred in 1/22 versus 5/18 participants during enteral-feeding follow-up (reported p = 0.04). The continuous group was more severely ill at baseline, and the small number of deaths made this unadjusted comparison an uncertain estimate of the feeding effect. Yao et al. (2025) reported hospital deaths in 6/65 versus 9/69 participants (p = 0.484), without significant differences in the ICU or hospital length of stay. Goksu and Tuncel did not evaluate mortality or length of stay as outcomes; their exclusion criteria included death and clinical deterioration, further limiting safety inference. The available event counts and follow-up do not establish equivalent safety or a survival advantage for any regimen.

Discussion

This review included four small, single-center randomized trials with 295 analyzed participants. Glycemic variability, the primary review outcome, was not reported using a common measure: within-day variation, seven-day SD, or coefficient of variation, serial glucose comparisons, and dysglycemic events answered different questions. Lower exogenous insulin requirements did not consistently coincide with lower variability. Gastrointestinal and nutritional findings also varied with definitions, schedules, and observation periods. Interpretation is further limited by incomplete result-level risk-of-bias documentation and the absence of an outcome-level certainty assessment. The evidence therefore supports a cautious description of regimen-specific findings rather than a preferred feeding strategy.

These findings broadly agree with previous systematic reviews in showing that the optimal feeding pattern remains uncertain, although they provide additional insight into metabolic outcomes that have been less extensively examined in earlier syntheses. Heffernan et al. found no clinically relevant differences between continuous and intermittent feeding for most outcomes, apart from a higher risk of constipation with CEN, and emphasized the limited availability of high-quality RCT evidence (Heffernan et al., 2022). Similarly, Abdelbaky et al. (2024) found no significant differences in diarrhea, constipation, vomiting, abdominal distension, aspiration, gastric residual volume, mortality, or length of stay between bolus and continuous feeding (Abdelbaky et al., 2024). In contrast, Ma et al. (2021) reported more feeding intolerance, high gastric residual volume, and aspiration with intermittent feeding, although IEN was associated with less constipation and greater caloric intake; importantly, the certainty of that evidence was rated low or very low (Ma et al., 2021).

More recent syntheses have produced conflicting results. Qu et al. (2023) associated IEN with more diarrhea and abdominal distension, longer ICU stay, but less constipation, whereas Wang et al. (2026) found no significant differences for most gastrointestinal or clinical endpoints apart from increased constipation with continuous feeding. Zhang et al. (2026) similarly reported more diarrhea and abdominal distension and a modestly longer ICU stay with IEN, but less constipation and no significant difference in ICU mortality, vomiting, gastric retention, aspiration pneumonia, or nutritional goal achievement. Thus, the potential advantages of IEN appear to include the provision of feeding-free periods, fewer interruptions in some protocols, lower insulin requirements in selected studies, and reduced constipation, whereas possible disadvantages include transiently greater glycemic fluctuations and gastrointestinal symptoms such as diarrhea or abdominal distension (Zhang et al., 2026). The present findings, however, suggest that these effects should not be attributed simply to "intermittent feeding" as a single intervention; rather, bolus volume, infusion duration, frequency, overnight fasting, and transition strategy may substantially modify its physiological effects.

Differences in feeding schedules offer plausible explanations for heterogeneous metabolic findings, but these mechanisms remain incompletely tested (Wu et al., 2023; Panwar et al., 2025). Diurnal feeding and nocturnal pauses create feeding-free periods, whereas four infusions at six-hour intervals do not necessarily align feeding with the daytime. Beattie et al. (2025) measured postprandial hormonal responses, but higher peak insulin and greater first-day glucose variability do not establish improved insulin sensitivity or circadian alignment. Likewise, lower exogenous insulin requirements in Goksu and Tuncel (2025) and Yao et al. (2025) cannot confirm either mechanism. Effects on gastrointestinal hormones, circadian regulation, insulin resistance, or muscle protein synthesis remain hypotheses unless directly measured. Differences in population, nutrient exposure, sampling frequency, and treatment protocols provide alternative explanations.

An important insight from this review is that the configuration of the feeding regimen may help explain differences in outcomes beyond the broad distinction between intermittent and continuous feeding. The four RCTs evaluated distinct protocols: three daily feeds with overnight fasting, daytime feeding with a nocturnal pause, four one-hour infusions at six-hour intervals, and a sequential transition from continuous to intermittent feeding after patients had achieved ≥80% of their energy target (Beattie et al., 2025; Goksu & Tuncel, 2025; Saiz-Vinuesa et al., 2025; Yao et al., 2025). These differences may partly explain the more stable glucose profile reported by Goksu and Tuncel (2025) compared with the greater glucose variability observed by Beattie et al. (2025) and Yao et al. (2025).

However, differences in patient populations, glucose measurement methods, and observation periods limit direct comparisons, and the contribution of individual protocol features cannot be isolated. Gastrointestinal findings also varied across trials without consistently favoring either feeding modality. Studies reporting nutritional delivery or target attainment generally found no statistically significant between-group differences, although this does not establish equivalent nutritional adequacy; in Yao et al. (2025), achievement of ≥80% of the energy target was a prerequisite for randomization. Yao et al. (2025) also reported higher serum albumin concentrations and exploratory differences in gut microbial composition and immune marker levels. These findings warrant further investigation but do not establish that feeding periodicity improves microbial, metabolic, or immune function.

The included trials do not validate a patient-selection or transition algorithm. Their findings should therefore not be used to assign continuous or intermittent feeding solely on the basis of mechanical ventilation, illness phase, glucose pattern, or achievement of a particular energy threshold. The ≥80% threshold in Yao et al. was a trial eligibility condition, not a validated clinical switching rule. Decisions in practice require assessment of the individual patient and applicable clinical guidance; guideline recommendations cited in the Introduction are external to this review. The present synthesis cannot establish the optimal schedule, infusion rate, or duration of overnight fasting.

Several limitations affect the interpretation. The review was not prospectively registered, limiting verification that eligibility, outcome priorities, and analytic decisions were established

before the findings were known. Searches were restricted to three databases, English-language publications, and the preceding five years; the Europe PMC full-text filter and absence of systematic registry or reference-list searching may have omitted relevant trials. Requiring a glycemic outcome also restricts the secondary safety evidence. All included trials were single-center studies with heterogeneous populations, feeding schedules, glucose measurements, gastrointestinal definitions, and follow-ups. Missing data and differences between randomized and analyzed populations may bias estimates; unblinded management and uncertainty about prespecified analyses raise additional concerns. The study-level RoB 2 summary does not establish risk of bias for each result, and GRADE was not performed. No pooled effects were estimated, and the narrative synthesis remains susceptible to selective emphasis on significant results from small trials. These limitations prevent firm conclusions about superiority, equivalent safety, or the optimal feeding regimen.

Conclusion

Available randomized trials are insufficient to determine whether intermittent or sequential enteral nutrition is superior to continuous feeding in critically ill adult patients. Glycemic and gastrointestinal findings vary across regimens, and lower insulin requirements do not necessarily indicate lower glucose variabilities. Non-significant findings do not establish equivalent effectiveness or safety and do not exclude clinically important differences between groups. This review does not support a validated feeding-selection algorithm or a preferred regimen.

Future multicenter trials should prespecify feeding schedules, glucose-monitoring methods and variability metrics, delivered energy and protein, gastrointestinal events, aspiration, mortality, and other patient-centered outcomes. They should report complete participant flow, address missing data, and prespecify clinically relevant subgroup analyses, including diabetes status and disease severity.

Declaration of Conflict Interests

The authors declare no conflicts of interest related to the research, authorship, or publication of this study.

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