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ORIGINAL COMMUNICATION

Combination of enteral and parenteral nutrition in the acute phase of critical illness: An updated systematic review and meta-analysis

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Abstract

Background: Uncertainty remains about the best route and timing of medical nutrition therapy in the acute phase of critical illness. Early combined enteral nutrition (EN) and parenteral nutrition (PN) may represent an attractive option to achieve recommended energy and protein goals in select patient groups. This meta-analysis aims to update and summarize the current evidence.

Methods: This systematic review and meta-analysis includes randomized controlled trials (RCTs) targeting the effect of EN alone vs a combination of EN with PN in the acute phase of critical illness in adult patients. Assessed outcomes include mortality, intensive care unit (ICU) and hospital length of stay (LOS), ventilation days, infectious complications, physical recovery, and quality-of-life outcomes.

Results: Twelve RCTs with 5543 patients were included. Treatment with a combination of EN with PN led to increased delivery of macronutrients. No statistically significant effect of a combination of EN with PN vs EN alone on any of the parameters was observed: mortality (risk ratio = 1.0; 95% CI, 0.79–1.28; $P = .99$), hospital LOS (mean difference, −1.44; CI, −5.59 to 2.71; $P = .50$), ICU LOS, and ventilation days. Trends toward improved physical outcomes were observed in two of four trials.

Conclusion: A combination of EN with PN improved nutrition intake in the acute phase of critical illness in adults and was not inferior regarding the patients' outcomes. Large, adequately designed trials in select patient groups are needed to answer the question of whether this nutrition strategy has a clinically relevant treatment effect.

KEYWORDS
critical illness, enteral nutrition, malnutrition, meta-analysis, nutrition therapy, parenteral nutrition, systematic review

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CLINICAL RELEVANCY STATEMENT

Medical nutrition therapy in the intensive care unit (ICU) is recognized as an important factor in the treatment of critically ill patients, but uncertainty remains about the best route and timing—especially in the acute phase of critical illness. Early combined enteral nutrition (EN) and parenteral nutrition (PN) may represent an attractive option to achieve recommended energy and protein goals in select critically ill patients. Previous meta-analyses included different patient groups and nonrandomized trials and did not include the two most recent trials on this topic, necessitating an update. Our updated systematic review and meta-analysis revealed that the use of a combination of EN with PN, as opposed to EN alone, improved nutrition delivery in the early phase of critical illness, but this did not translate into a statistically significant impact on the meta-analyzed end points of mortality, hospital or ICU length of stay, or duration of mechanical ventilation. A combination of EN with PN was associated with a tendency toward reduced mortality in subgroup analysis evaluating patients at nutrition risk, and trends were observed for improved functional outcomes. Accordingly, a combined approach of EN with PN cannot be recommended with high evidence in all patients but may be effective to increase nutrition delivery, indicating a promising strategy for patients in whom continued underfeeding with EN alone may result in significant harmful nutrition deficiencies.

INTRODUCTION

Critically ill patients in the intensive care unit (ICU) are at significant risk of underfeeding, which is associated with poor clinical outcomes and increased risk of mortality.[1] In addition, critically ill patients have a high prevalence of risk factors for malnutrition, including age, weight loss, inflammation, severity of disease, and history of reduced food intake.[2] During the past decades until today, the optimal feeding route in critically ill patients has remained controversial.[3] Medical nutrition therapy (MNT) encompasses oral nutrition, enteral nutrition (EN), and parenteral nutrition (PN), or a combination of these forms in critically ill patients.

Current international nutrition guidelines uniformly recommend early EN within 24–48 h after ICU admission in critically ill patients who are unable to maintain sufficient oral intake.[4–6] The physiologic advantages of EN are translated into reduced infectious complications, shortened ICU and hospital length of stay (LOS), and reduced overall mortality.[7–9] However, EN alone is often insufficient to achieve energy and protein targets within the acute phase of critical illness, mainly the first week after ICU admission.[10–12] Factors contributing to the slow progress of EN into a full feeding rate are hemodynamic instability, gastrointestinal intolerance, and frequent interruptions of EN,[13–17] which ultimately may lead to significant nutrition deficiencies.

Over the past years, the concerns about PN-associated complications such as overfeeding, hyperglycemia, and hyperlipidemia have impeded the frequent use of PN in clinical settings, and international nutrition guidelines have not recommended the routine use of PN in the early phase of critical illness.[5,8,18–20] However, recent studies have shown that PN itself, or a coadministration of EN and PN, may yield results comparable to those of EN alone or may even be superior in critically ill patients with prolonged hemodynamic instability.[21,22]

Recommended protein and energy targets are still debated and controversial, as recent randomized and observational trials have yielded contradictory results, with a growing trend that less energy and protein delivery may be more beneficial in the early acute phase of critical illness.[23] However, a combined use of EN with PN might help achieve the desired nutrition targets rapidly and safely[1,24,25] and could be considered in patients at high nutrition risk in whom the nutrition targets could not be met by EN alone.[5] In this context, several randomized controlled trials (RCTs) have investigated the effect on clinical outcomes of a combination of EN with PN in critically ill patients and have shown significant clinical relevance for critically ill patients. However, there is considerable heterogeneity between these trials regarding patient population, timing, and dosing of MNT, which may be one reason for previous meta-analyses to yield contradicting results.[26–29] Another reason may be that none of the current analyses[26,27,30,31] differentiate between two administration strategies: early combined EN and PN (EN+PN) or supplementary PN (SPN), in which EN is supplemented by PN after some period if full EN is impossible or fails to reach nutrition targets. Nevertheless, these two administration strategies that combine EN with PN may have different clinical implications, which is investigated in this analysis. Additionally, none of the existing meta-analyses include both the most recent trials and trials by Ridley et al[32] and Berger et al,[33] underlining the importance of this updated review and meta-analysis. Therefore, this systematic review and meta-analysis aims to provide an up-to-date investigation of the influence of any combination of EN with PN (either early EN+PN or delayed SPN) compared with that of EN alone on clinically relevant outcomes in the acute phase in severely critically ill patients.

METHODS

This systematic review was registered at the PROSPERO international database on May 5, 2020 (registration number: CRD42020184355). This systematic review was performed according to Cochrane Standard, and the reporting is in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy

We included RCTs comparing the effect of EN alone vs a combination of EN with PN (either EN+PN or SPN) regarding the clinical outcomes of critically ill patients. Relevant trials were identified through a systematic search of the databases Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). Reference lists of included studies and personal files were searched as well. There were no language restrictions on included studies. Unpublished manuscripts were included in the review process. Data reported as

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abstracts only were excluded. The inclusion criteria were based on the PICOS acronym (Patient, Intervention, Comparison, Outcome, Study type).[34] The search was conducted on May 8, 2020. All publications published until then in at least one of these databases were included. The systematic search included the following terms to be found in the title or abstract:

- "Critical Care" OR "Intensive care" OR "critically ill" OR "critical illness" OR "ICU patients"
- "Parenteral nutrition" OR "supplemental parenteral nutrition" OR "enteral nutrition" OR "supplemental enteral nutrition" OR "enteral feed*" OR "parenteral feed*" OR "artificial feed*" OR "artificial nutrition" OR "artificial supplementation" OR "intravenous supplementation"
- "Clinical trial" OR "randomized" OR "randomized controlled trial" OR "RCT" OR "randomly"

Study selection criteria

Studies were selected for inclusion in the review process if they met the following criteria:

- Population: Critically ill adult patients (≥18 years). For this review process, we defined a critically ill patient as a patient cared for in an ICU-environment who (1) required mechanical ventilation or (2) had urgent or life-threatening complications (≥5% baseline mortality rate) in order to distinguish them from patients with elective surgery, who also are cared for in some ICUs but have a low baseline mortality rate. Patients with a scheduled ICU stay after elective surgery were excluded.
- Intervention group: Patients receiving any combination of EN with PN or intravenous nutrients.
- Control group: Patients receiving EN alone.
- Outcomes: Mortality (ICU, hospital, long term), LOS in the ICU and hospital, duration of mechanical ventilation, quality of life, physical outcomes, and complications. If the studies reported at least one of these outcomes, they were included in the review process. Owing to the heterogeneity of the time point of mortality in the different trials, mortality is reported in this analysis as "within 30 days after admission to ICU."
- Study design: RCTs; when treatment allocation in an RCT was not truly random, such as assigning a treatment intervention based on day of admission or based on the hospital admission number (pseudorandomized trials), these trials were excluded. Reviews, systematic reviews, and meta-analyses were included in the review process for the purpose of cross-referencing.

Selection of studies

Of the identified potential studies, a database was constructed using the reference manager EndNote X9 (Clarivate Analytics, Boston, MA). After identification and removal of duplicates, titles and abstracts were screened by two independent reviewers (A.H. and E.L.). Relevant full texts were retrieved and screened independently by two reviewers (A.H. and D.K.H.) as well to identify studies for inclusion and to document the reasons for exclusion of the ineligible studies (Table S1). If there were any disagreements, a third author (C.S., G.E., L.A.O.R., or S.W.) was asked to arbitrate. Duplicates were identified and excluded; multiple reports of the same study were collated so that each study, rather than each report, was the unit of interest in the review. Authors were contacted to obtain missing full texts in June 2019, May 2020, and June 2020 (A.H. and L.A.O.R.).

Data extraction and management

Articles published in languages other than English were translated.[35,36] Two review authors independently extracted outcome data from included studies (A.H. and L.A.O.R.). Authors of primary studies were contacted for supplementary information or clarification, if necessary (June 2019, May 2020, and June 2020) . For each trial, the following descriptors were abstracted: intervention, study population, nature of allocation, cointerventions, exclusions after randomization, double-blinding, event rates, relative risk, and other outcomes. The data were transferred into the Review Manager (Review Manager 5, version 5.3, The Nordic Cochrane Centre) software. The correct entering of the data was double-checked by comparing the data presented in the systematic review with the data extraction form, and the second review author spot-checked study characteristics for accuracy against the trial report.

Quality assessment for each RCT

Two authors (L.A.O.R. and A.H.) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (random sequence generation; blinding of participants and personnel; blinding of outcome assessment; allocation concealment; incomplete outcome; selective reporting; and other bias), assessing low risk, high risk, or unclear risk of bias. Analyses of the data and figures were computed using the RevMan 5.3 software. Disagreements were solved by discussion with a third author (C.S. or D.K.H.).

Measures of treatment effect

Dichotomous data were analyzed as risk ratios (RRs) with 95% CIs. For continuous data, the mean difference (MD) with 95% CI for outcomes measured in the same way between trials was used as implemented in RevMan 5.3 software. Analyses were carried out on an intention-to-treat (ITT) and sensitivity basis for all outcomes. Statistical analysis was performed using the RevMan 5.3 software. Meta-analyses were undertaken only when this was meaningful—that is, if the treatments,

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participants, and underlying clinical questions were similar enough for pooling to make sense. Missing means and standard deviations for Casaer et al[37] were calculated from test statistics using the methods proposed by Luo et al.[38] Given the clinical heterogeneity regarding present inclusion criteria (different types of patients and timing of intervention), random-effects meta-analyses were used to produce an overall summary of average treatment effect across trials. Results are presented as the average treatment effect with its 95% CI and the estimates of Tauš and Iš.

A priori, we considered several situations in which MNT may have a variable effect and explored the following subgroups analyses:

- Trials of patients receiving EN+PN vs EN alone compared with trials of patients receiving SPN vs EN alone, as these are different strategies regarding the timing of PN and may have a different clinical effect
- Trials published until 2000 compared with trials published later than 2000, as "major relevant changes were implemented after new scientific data became available around the start of the new millennium"[4]
- Trials recruiting patients at increased risk for malnutrition or nutrition risk compared with trials that included heterogenous groups of patients without consideration of nutrition status, as these different patient populations may respond differently to nutrition therapy

Because in two trials (Casaer et al[39] and Chiarelli et al[36]), intravenous nutrients were given in both groups, sensitivity analyses were performed with these trials excluded.

RESULTS

Study selection process

The search identified 910 potential trials. Twenty-one additional articles were found during cross-referencing and from the authors' own reference collections. After removal of three duplicates, 928 manuscripts underwent title and abstract screening, and 51 trials underwent full-text screening. A list of the manuscripts that were excluded after full-text screening and the reasons for exclusion are provided in the Table S1. Details of the study selection process are shown in Figure S1. Twelve studies met the inclusion criteria of our review and underwent data extraction; the study characteristics and clinical outcomes are shown in Table 1.[32,33,35–37,40–46]

Risk of bias across all RCTs

Fifty percent (6/12) of the RCTs reported adequate generation of the random sequence, 46% (5/12) of the RCTs reported adequate allocation sequence concealment, and 8% (1/12) of the included RCTs reported adequate blinding of the outcome assessors. A graph of the risk of bias and the assessment of each RCT are shown in Figures S2 and S3.

Clinical outcomes

Patient population

The patients included in this analysis represent different populations among critically ill patients. Seven RCTs included patients without nutrition risk assessment: two RCTs including severely burned patients,[44,45] one RCT including trauma patients,[42] and four RCTs including a mixed cohort.[32,33,36,43] The other five RCTs included patients evaluated to be at nutrition risk: two trials including patients with anticipated low food intake,[40,41] one RCT including patients with diminished food intake during the first days after admission,[37] one RCT including patients with a body mass index (BMI) <25 or >35 kg/m^2,[46] and one study focusing on elderly patients with respiratory diagnoses,[35] who are prone to chronic malnutrition.[2]

Delivery of nutrients

Trials reported nutrition data in a nonuniform manner (Table 2), which precluded statistical aggregation. Hence, we report the overall results qualitatively. A combination of EN with PN, compared with EN alone, significantly increased energy intake in six trials,[32,33,41,43,44,46], whereas differences between groups were not observed in two trials.[36,42] Regarding protein, significant increases of delivery in groups receiving a combination of EN with PN were observed in four trials,[32,33,43,46] whereas one trial reported no difference.[42]

Thirty-day mortality

All 12 RCTs reported the outcome of 30-day mortality as shown in Figure 1. On average, no significant effect of any combination of EN with PN on "mortality within 30 days" was observed (RR = 1.0; 95% CI, 0.79–1.28; $P = .99$), with low to moderate statistical heterogeneity ($I^2 = 30\%$). A subgroup analysis in a single trial did demonstrate a tendency toward lower mortality in patients at high nutrition risk when EN+PN was provided ($P = .19$ in patients with Nutrition Risk in the Critically Ill [NUTRIC] score ≥5 and BMI <25 kg/m^2).[46] In our subgroup analyses, no difference in treatment effect was observed in RCTs using EN+PN vs those using SPN (test for subgroup differences, $P = .72$) in RCTs published until 2000 vs those published after 2000 (test for subgroup differences, $P = .18$), and no difference was observed in trials including patients with or without a baseline nutrition risk assessment (test for subgroup differences, $P = .28$). There were no statistically significant differences in clinical outcomes between the ITT and sensitivity analyses, but there was an apparent large treatment effect in the subgroup

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TABLE 1 Randomized studies evaluating a combination of EN with PN in critically ill patients

Study	Population	Intervention	Cointervention	Study period
Trials comparing EN and PN with EN				
Herndon 1987[44]	28 patients with burns >50% TBSA	EN+PN vs EN	Albumin and hourly feedings (milk or commercial EN) for all	Day 0–10 after injury
Herndon 1989[45]	39 patients with burns >50% TBSA	EN+PN vs EN	Albumin and hourly feedings (milk or commercial EN) for all	NR, presumably day 0–14 after injury
Dunham 1994[42]	37 blunt-trauma patients	EN+PN vs EN vs PN[a]; PN made up 50% of given energy	NR	Randomized <30 h after injury
Chiarelli 1996[33]	24 ICU patients, medical and surgical	EN+PN vs EN; PN made up 50% of given energy; PN for all patients on days 1–3	NR	Intervention starting day 4, duration NR
Bauer 2000[40]	120 patients expected to eat <20 kcal/kg daily for 2 days	EN+PN vs EN+placebo PN: 120 ml/h of 1 kcal/ml for 18–24 h. EN: bolus feeding up to 350 ml of 1-kcal/ml standard formula	GRV > 300 ml: feeding delayed by 4 h and cisapride was added	Started early, continued for 4–7 days
Abrishami 2010[39]	20 SIRS patients with APACHE II >10 and expected not to feed orally for ≥5 days	EN+PN vs EN. EN+PN: EN + 500 ml of 10% amino acid solution + 500 ml of dextrose 50% solution	Metoclopramide if GRV > 300 ml	Days 1–7 after admission
Casaer 2011[35,48]	2312 ICU patients, NRS > 3; all patients who were unable to eat by day 2 received EN and were expected to remain on ICU for >5 further days	EN+PN vs EN. EN+PN: 20% glucose solution (400 kcal day 1, 800 kcal day 2); day 3: EN+PN at 100%, when EN covered 80% or patient was fed orally, PN was reduced/stopped. PN was restarted whenever enteral or oral intake fell to <50% of the calculated energy needs	Prokinetic agents	Days 1–7 but PN not started until day 3
Chen 2011[32]	147 elderly patients in respiratory ICU	EN+PN vs EN vs PN.[a] PN to make up energy and nitrogen deficit; EN: 100 ml/h = goal rate	Metoclopramide if GRV > 200 ml, NJ if not tolerating NG	NR, comparison of groups on day 7
Wischmeyer 2017[47]	125 adult (≥18 years) mixed ICU patients with BMI <25 or >35, mNUTRIC score <5 or >5	EN+PN vs EN. PN adjusted daily to reach 100% of goal energy, in extubated patients, until 50% of energy goal was tolerated orally	No	Days 1–7 or until death
Trials comparing SPN with EN				
Heidegger 2013[43]	305 ICU patients requiring treatment >5 days, not achieving 60% of calculated energy target by end of day 3	SPN vs EN. EN progression encouraged in both groups	Prokinetic agents (≥300 ml)	4–8 days after randomization and 28-day follow-up
Ridley 2018[46]	100 adult (≥16 years old) mixed ICU patients not achieving 80% of target within first 48–72 h of admission	SPN vs EN. SPN to provide 80% of goal energy based on amount of EN received	No	7 days or until ICU discharge/oral nutrition
Berger 2019[41]	23 mechanically ventilated patients who by end of day 3 did not receive >60% of equation target	SPN vs EN. EN alone for all patients days 1–3	No	6 days after randomization and 15 and 28 days' follow-up

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TABLE 1 (Continued)

Study	Mortality[a,c] (%)		Infections[a,d] (%)		LOS in days		Ventilator days		Other	
	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN
Trials comparing EN+PN with EN										
Herndon 1987[44]	8/13 (62)	8/15 (53)	NR	NR	NR	NR	NR	NR	NR	NR
Herndon 1989[45]	Day >14: 10/16 (63)	Day >14: 6/23 (26)	NR	NR	NR	NR	NR	NR	NR	NR
Dunham 1994[42]	3/10 (30)	1/12 (8.3)	NR	NR	NR	NR	NR	NR	Nutrition-related complications: 5/10 (50)	Nutrition-related complications: 3/12 (25)
Chiarelli 1996[33]	3/12 (25)	4/12 (33)	Bloodstream: 5/12 (42) Bronchial aspirate: 7/12 (58) Positive chest x-ray: 6/12 (50)	Bloodstream: 5/12 (42) Bronchial aspirate: 6/12 (50) Positive chest x-ray: 3/12 (25)	Hospital: 37 ± 13	Hospital: 41 ± 23	19 ± 6	19 ± 2	NR	NR
Bauer 2000[40]	Day >4: 3/60 (5)90-day: 17/60 (28)	Day >4: 4/60 (6.7)90-day: 18/60 (30)	39/60 (65)	39/60 (65)	ICU: 16.9 ± 11.8Hospital: 31.2 ± 18.5	ICU: 17.3 ± 12.8Hospital: 33.7 ± 27.7	11 ± 9	10 ± 8	Glycemia on day 7 (g/L): 1.16 ± 0.36	Glycemia on day 7 (g/L): 1.31 ± 0.49
Abrishami 2010[39]	2/10 (20)	1/10 (10)	NR	NR	ICU: 25.7Hospital: 37.4	ICU: 27.7Hospital: 36.5	NR	NR	NR	NR
Casaer 2011[35,48]	ICU: 146/2312 (6.3) Hospital: 251/2312 (10.9) Within 90 days after enrollment: 255/2312 (11.2)	ICU: 141/2328 (6.1) Hospital: 242/2328 (10.4) Within 90 days after enrollment: 257/2328 (11.2)	Any: 605/2312 (26.2) Airway or lung: 447/2312 (19.3) Bloodstream: 174/2312 (7.5) Wound: 98/2312(4.2)Urinary tract: 72/2312 (3.1)	Any: 531/2328 (22.8) Airway or lung: 381/2328 (16.4) Bloodstream: 142/2328 (6.1) Wound: 64/2328 (2.7)Urinary tract: 60/2328 (2.6)	ICU: 5.05 ± 5.19; 4 [2–9] Hospital: 18.1 ± 14.83; 16 [9–29]	ICU: 4.05 ± 3.7; 3 [2–7] Hospital: 16.8 ± 13.35; 14 [9–27]	2.7 ± 2.96; 2 [1–5]	2.7 ± 2.96; 2 [1–5]	Kidney failure median duration (days) of renal replacement therapy: 10 [5–23]	Kidney failure median duration (days) of renal replacement therapy: 7 [3–16]

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TABLE 1 (Continued)

Study	Mortality[a,c] (%)		Infections[a,d] (%)		LOS in days		Ventilator days		Other	
	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN	Combination of EN and PN	EN
Chen 2011[32]	20-day: 3/49 (6)	20-day: 11/49 (22)	6/49 (12)	5/49 (10)	ICU: 6.75 ± 1.8Hospital: 17.3 ± 2.5	ICU: 9.1 ± 2.8Hospital: 23.32 ± 5.6	5.76 ± 1.56	8.0 ± 2.1	"Other complications": 8/49 (16)	"Other complications": 10/49 (20)
Wischmeyer 2017[47]	ICU: 7/52 (13.5)Hospital: 8/52 (15.4)	ICU: 13/73 (17.8)Hospital: 17/73 (23.3)	38/52	46/73	ICU[b]: 16.7 ± 13.5 Hospital[b]: 39.9 ± 61.9	ICU[b]: 14.2 ± 9.2 Hospital[b]: 29.6 ± 22.6	11.1 ± 11.3[b]	10.4 ± 8.7[b]	NR	NR
Trials comparing SPN with EN										
Heidegger 2013[43]	ICU: 8/153 (5)28-day: 20/153 (13)	ICU: 11/152 (7)28-day: 28/152 (18)	Day: 4–28please delete the b here 77/153 (50)	Day: 4–28 please delete the b here; 85/152 (56)	ICU: 13 ± 10Hospital: 31 ± 23	ICU: 13 ± 11Hospital: 32 ± 23	2.5 ± 4.6	2.8 ± 4.2	Similar glucose control in the EN+PN and EN groups, target < 8 mmol/L	
Ridley 2018[46]	ICU: 15/51 Hospital: 16/51 90-day: 19/51180-day: 19/51	ICU: 11/48Hospital: 11/48 90-day: 13/48180-day: 13/48	NR	NR	ICU[b]: 13 ± 10Hospital: 22 ± 21	ICU[b]: 13.9 ± 11.7Hospital: 23 ± 17	12.2 ± 8.3[b]	12.8 ± 10.1[b]	Vomiting: 3/51	Vomiting: 18/48
Berger 2019[41]	0/11 (0)	1/12 (8.3)	1 [1–1]: n = 11	1 [1–2]: n = 12	ICU: 16.01 ± 8.09; 15.3 [10.6–17.4] Hospital: 45.36 ± 20.51; 44 [30–57]	ICU: 15.74 ± 12.74; 9.5 [7.1–24.4] Hospital: 46.91 ± 25.13; 48 [25–59]	11 ± 7.66; 8.9 [4.9–15.7]	9.5 ± 8.5; 5.5 [4.2–14.5]	AUC of glycemia did not differ between groups; net protein breakdown similar to 0 in both groups	

Abbreviations: AUC, area under the curve; APACHE II, Acute Physiology And Chronic Health Evaluation II; BMI, body mass index; EN, enteral nutrition; GRV, gastric residual volume; ICU, intensive care unit; ; LOS, length of stay; NG, nasogastric tube; NJ, nasojejunal tube; NR, not reported; NRS, Nutrition Risk Screening; mNUTRIC score, modified Nutrition Risk in the Critically Ill score; PN, parenteral nutrition; SIRS, systemic inflammatory response syndrome; SPN, supplementary PN; TBSA, total body surface area.

[a]Only EN+PN vs EN groups are included in this analysis.

[b]Data obtained from author as mean and standard deviation.

[c]Presumed hospital mortality unless otherwise specified, + mean ± standard deviation.

[d]Refers to the number of patients with infections unless specified.

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TABLE 2 Delivery of nutrients

Study	Energy target	Energy delivered			Protein target	Protein delivered		
		Combination EN and PN	EN	Comparison between groups: *P*-value		Combination EN and PN	EN	Comparison between groups: *P*-value
Trials comparing EN+PN with EN								
Herndon 1987[44]	25 kcal/kg/day + 40 kcal/%TBSA	Day 0–3: 3421 ± 336 kcal/day Days 4–7: 3997 ± 304 kcal/day Days 8–10: 4191 ± 485 kcal/day	Day 0–3: 321 ± 177 kcal/day Days 4–7: 1494 ± 358 kcal/day Days 8–10: 1876 ± 541 kcal/day	<.05 for days 0–7; NS for days 8–10	NR	NR	NR	–
Herndon 1989[45]	25 kcal/kg/day + 40 kcal/%TBSA	Survivors: 3080 ± 177 kcal/day Nonsurvivors: 2952 ± 415 kcal/day	Survivors: 1994 ± 217 kcal/day Nonsurvivors: 498 ± 422 kcal/day	<.05; between survivors and nonsurvivors	NR	NR	NR	–
Dunham 1994[42]	1.3 × basal energy expenditure by HBE	Days 1–7: 2067 ± 499 kcal/day (n = 3)	Days 1–7: 2097 ± 552 kcal/day (n = 6)	NS	1.75 g/kg/day	Days 1–7: 222 ± 31 g (n = 3)	Days 1–7: 129 ± 35 g (n = 6)	NS
Chiarelli 1996[33]	NR	31 ± 6 kcal/kg/day	33 ± 9 kcal/kg/day	NS difference of lost energy	NR	NR	NR	–
Bauer 2000[40]	25 kcal/kg/day	Day 4: 11 ± 3.3 kcal/kgDay 7: 14.8 ± 4.6 kcal/kg	Day 4: 9.9 ± 3.9 kcal/kgDay 7: 13.2 ± 4.3 kcal/kg	Day 4: .25Day 7: .6	1 g of N per 100 kcal of carbohydrate-fat	NR	NR	–
Abrishami 2010[39]	NR	NR	NR	–	NR	NR	NR	–
Casaer 2011[35,48]	Day 1: 400 kcal/day Day 2: 800 kcal/day Day 3: 100% kcal/dayMaximum goal: 2880 kcal/day	NR	NR	–	NR	NR	NR	–
Chen 2011[32]	NR	NR	NR	–	NR	NR	NR	–
Wischmeyer 2017[47]	BMI <25: 25 kcal/kg[a]/day BMI >35: 20 kcal/kg[b]/day	Days 0–7: 95% ± 13%Days 0–27: 90% ± 16%	Days 0–7: 69% ± 28%Days 0–27: 72% ± 25%	Days 0–7: <.001Days 0–27: <.001	BMI <25: 1.2 g/kg[a]/day BMI >35: 1.2 g/kg[b]/day	Days 0–7: 86% ± 16%Days 0–27: 82% ± 19%	Days 0–7: 64% ± 26%Days 0–27: 68% ± 25%	Days 0–7: <.001Days 0–27: <.001
Trials comparing SPN with EN								
Heidegger 2013[43]	Women: 25 kcal/kg[e]/day Men: 30 kcal/kg[e]/dayIC in 65% of patients	Days 4–8: 28 kcal/kg/day	Days 4–8: 20 kcal/kg/day	<.0001	1.2 g/kg/day	Days 4–8: 1.2 g/kg/day	Days 4–8: 0.8 g/kg/day	<.0001

(Continues)

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TABLE 2 (Continued)

Study	Energy target	Energy delivered		Comparison between groups: *P*-value	Protein target	Protein delivered		Comparison between groups: *P*-value
		Combination EN and PN	EN			Combination EN and PN	EN	
Ridley 2018[46]	25 kcal/kg/day, or, if on RRT or ECMO, 30 kcal/kg/day	7 days:calories from nutrition: 1712 ± 511 kcal/dayAll sources (including glucose and propofol): 1892 ± 54	7 days:calories from nutrition: 1130 ± 601 kcal/dayAll sources (including glucose and propofol): 1298 ± 671	7 days:nutrition: <.0001All sources: <.0001	Per standard/local practices	86 ± 35 g/day	53 ± 29 g/day	<.0001
Berger 2019[41]	Days 1–3: 25 kcal/kg/dayCalorimetry days 4 and 9	5 days of intervention: 4.3 kcal/kg/day	5 days of intervention: 16.1 kcal/kg/day	.006	1.2 g/kg[e]/day	1.16 g/kg/day	0.67 g/kg/day	.05

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; EN, enteral nutrition; HBE, Harris-Benedict equation; IC, indirect calorimetry; N, nitrogen; NR, not reported; NS, not significant; PN, parenteral nutrition; RRT, renal replacement therapy; SPN, supplementary PN; %TBSA, percentage of total body surface area.

[a]Kilograms of actual body weight.

[b]Kilograms of adjusted body weight.

[e]Kilograms of ideal body weight.

of trials that included patients with a nutrition risk assessment when excluding the Chiarelli and Casaer trials (RR = 0.71; 95% CI, 0.41–1.24; see Figure S4).

Hospital LOS

Eight studies including 5434 patients reported the outcome hospital LOS as shown Figure 2. On average, no significant effect of any combination of EN with PN on hospital LOS was observed (MD, −1.44; 95% CI, −5.59 to 2.71; $P = .50$), with substantial statistical heterogeneity ($I^2 = 88\%$). There was no difference in the treatment effect in RCTs using EN+PN vs those using SPN, RCTs published until 2000 vs those published after 2000, or RCTs including patients with or without a baseline nutrition risk assessment (test for subgroup differences, $P = .88$, $P = .97$, and $P = .99$). There were no statistically significant differences in clinical outcomes between the ITT and sensitivity analyses, but there was again a large treatment effect in the subgroup of trials that included patients with a nutrition risk assessment when excluding the Chiarelli and Casaer trials (MD, −3.4 days; 95% CI, −9.42 to 2.03; see Figure S5).

ICU LOS

Seven studies including 5410 patients reported the outcome ICU LOS as shown in Figure 3. On average, no significant effect of any combination of EN with PN on ICU LOS was observed (MD, −0.15; 95% CI, −2.05 to 1.75; $P = .88$) with substantial statistical heterogeneity ($I^2 = 88\%$). There was no difference in the treatment effect in RCTs using EN+PN vs those using SPN, RCTs published until 2000 vs those published after 2000, or RCTs including patients with or without a baseline nutrition risk assessment (test for subgroup differences, $P = .94$, $P = .91$, and $P = .94$). Sensitivity analysis showed no difference when the trials by Casaer et al and Chiarelli et al were excluded.

Duration of mechanical ventilation

Eight studies including 5434 patients reported the outcome duration of mechanical ventilation as shown in Figure 4. On average, no significant effect of any combination of EN with PN on the duration of mechanical ventilation (MD, −0.43; 95% CI, −1.50 to 0.63; $P = .42$) with substantial statistical heterogeneity ($I^2 = 79\%$) was observed. There was no difference in the treatment effect in RCTs using EN+PN vs those using SPN, RCTs published until 2000 vs those published after 2000, or RCTs including patients with or without a baseline nutrition risk assessment (test for subgroup differences, $P = .83$, $P = .31$, and $P = .79$) and no difference in sensitivity analysis.

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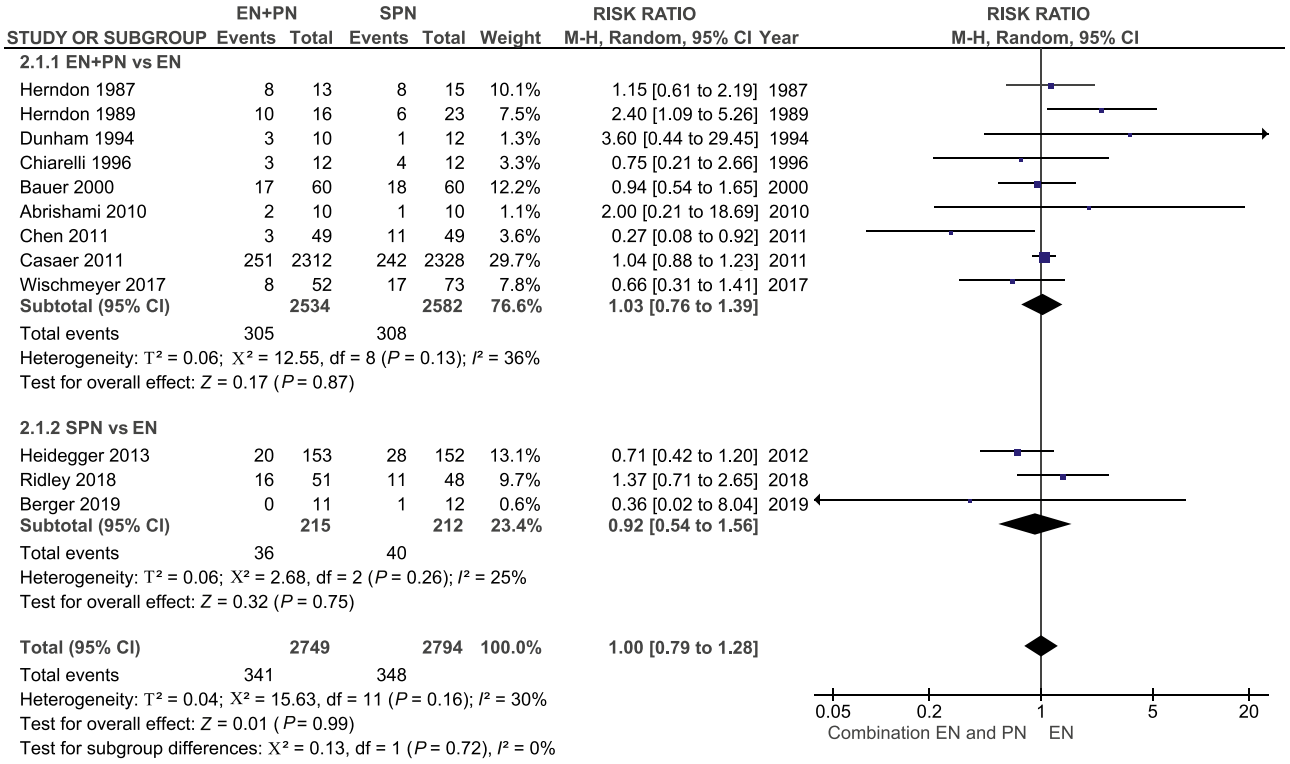

FIGURE 1 Mortality within 30 days (meta-analysis). EN, enteral nutrition; EN+PN, combined EN and PN; M-H, Mantel-Haenszel; PN, parenteral nutrition; SPN, supplementary PN

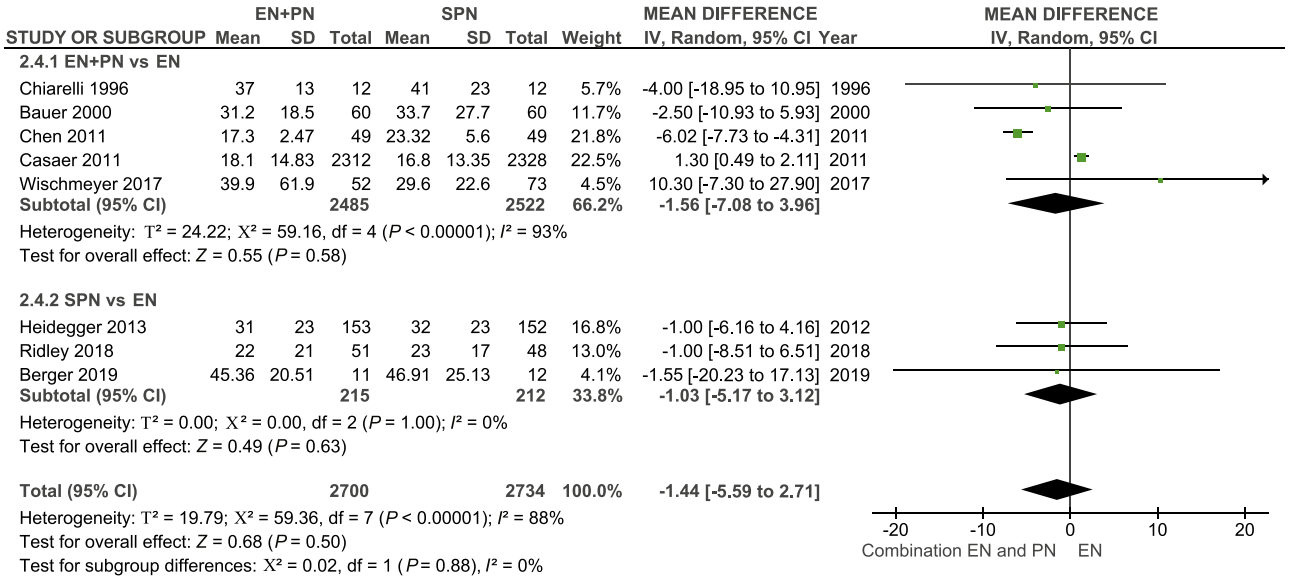

FIGURE 2 Hospital length of stay (meta-analysis). EN, enteral nutrition; EN+PN, combined EN and PN; IV, inverse variance; PN, parenteral nutrition; SD, standard deviation; SPN, supplementary PN

Infectious and glycemic complications

Seven trials reported on the outcome "infectious complications," but the time window for its assessment as well as the definition of infection was too heterogeneous to perform meta-analysis.

Differences between treatment groups were observed in three trials. An older RCT performed by Chiarelli et al[36] observed lower rates of pneumonia (50% infections in the EN+PN group [6/12] and 25% in the EN group [3/12]) as defined by positive bronchial aspirate and an x-ray of the chest. Casaer et al[39] observed significantly more

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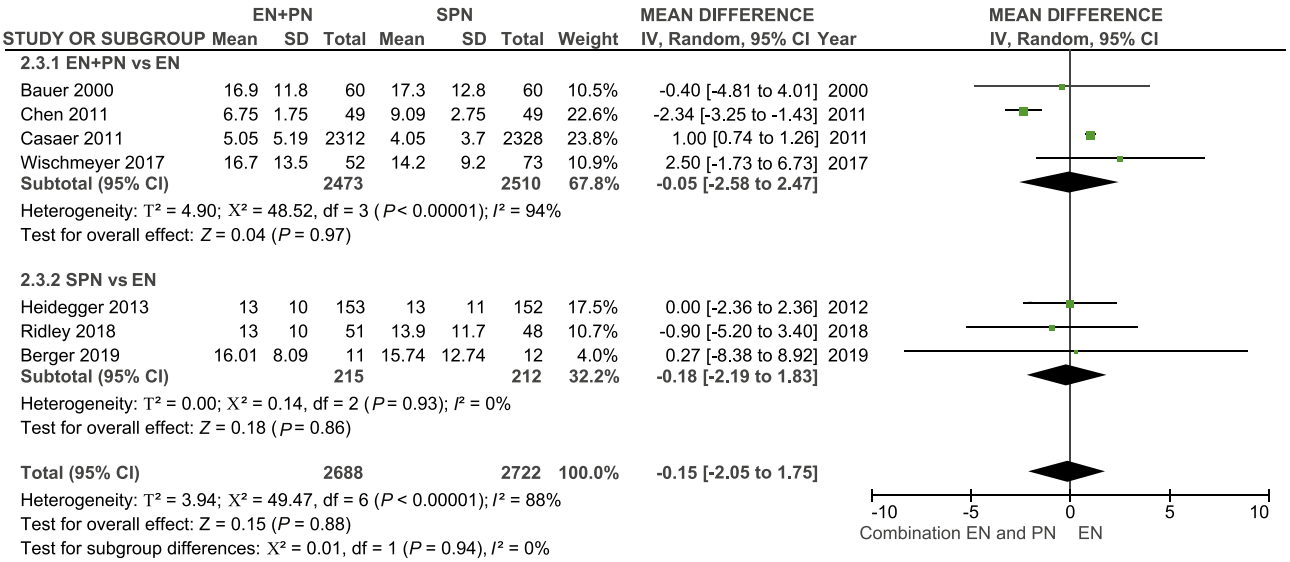

FIGURE 3 Intensive care unit length of stay (meta-analysis). EN, enteral nutrition; EN+PN, combined EN and PN; IV, inverse variance; PN, parenteral nutrition; SD, standard deviation; SPN, supplementary PN

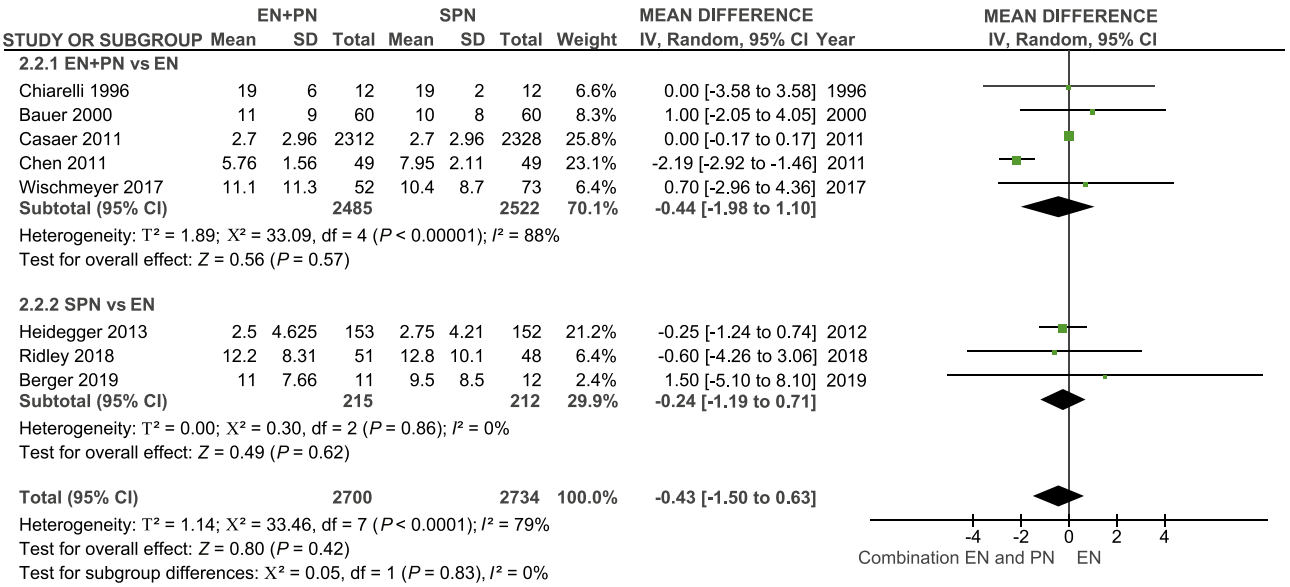

FIGURE 4 Duration of mechanical ventilation in days (meta-analysis). EN, enteral nutrition; EN+PN, combined EN and PN; IV, inverse variance; PN, parenteral nutrition; SD, standard deviation; SPN, supplementary PN

infections in the EN+PN group (P = .008), which included airway, bloodstream, wound, and urinary tract infections. Heidegger et al[43] reported a lower risk of nosocomial infection from days 9–18 in the SPN group in comparison with the group receiving EN alone (hazard ratio, 0.65; 95% CI, 0.43–0.97; P = .0338), and the SPN group had a lower mean number of nosocomial infections per patient (hazard ratio, −0.42; CI, −0.79 to −0.05; P = .0248). With the data obtained from the authors for days 4–28, no differences between groups were found (Table 1). No statistically significant differences regarding infection rates were observed in the other four trials that reported this outcome.[33,35,41,46]

Blood glucose levels were reported by four trials. Hyperglycemia was significantly more frequent on day 7 only in the EN+PN group compared with the group receiving EN alone in the RCT by Bauer et al (P < .05).[41] On the contrary, Chiarelli et al observed no difference in glycemia between the groups, but no numbers were reported.[36] Heidegger et al[43] reported similar glucose control in both groups, and Berger et al[33] reported similar areas under the curve for glycemia.

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TABLE 3 Physical outcomes

Study	Outcomes	Combination of EN and PN	EN alone	*P*-value
Chen 2011[32]	Changes in respiratory muscle strength before and after nutrition support[a], cm H_2O	Before: 28.34 ± 9.49 Day 7: 34.32 ± 15.43 *P* = .025	Before: 26.75 ± 11.6 Day 7: 32.3 ± 10.3 *P* = .011	
Wischmeyer 2017[47]	Handgrip strength[b], kg	ICU discharge: 9 (43) [unable–25] Hospital discharge: 12 (36) [unable–33]	ICU discharge: Unable (62) [unable–18] Hospital discharge: Unable (56) [unable–20]	.21.14
	6-Minute Walk Test at hospital discharge[b]	Unable (40) [unable–0]	Unable (60) [unable–unable]	.2
	Barthel index at hospital discharge[a]	61.1 ± 32.4 (28)	46.5 ± 32.1 (41)	.08
	SF-36: Standardized physical component scale[a]	3 months: 33.3 ± 10.1 (22) 6 months: 39.3 ± 10.2 (20)	3 months: 35.3 ± 10.8 (27) 6 months: 35.8 ± 11.2 (30)	.38 .17
	SF-36: Standardized mental component scale[a]	3 months: 51.5 ± 10.0 (22) 6 months: 49.0 ± 13.5 (20)	3 months: 50.0 ± 10.5 (27) 6 months: 43.2 ± 14.8 (30)	.38 .11
Ridley 2018[46]	Handgrip strength at hospital discharge[a], kg	19 ± 13.5 (19)	20 ± 8 (24)	.71
	ICU mobility scale at hospital discharge[b]	9 (25) [5–10]	8 (33) [4–10]	.58
	EQ-5D-3L[a]	Hospital discharge: 0.25 ± 0.34 (27) 90 days: 0.69 ± 0.24 (35) 180 days: 0.75 ± 0.26 (35)	Hospital discharge: 0.32 ± 0.36 (17) 90 days: 0.76 ± 0.23 (29) 180 days: 0.77 ± 0.2 (29)	.54 .29 .76
Berger 2019[41]	Difference in quadriceps cross-sectional area between days 4 and 15 after admission	−16%	−21%	.07

Abbreviations: EN, enteral nutrition; ICU, intensive care unit; PN, parenteral nutrition; SF-36, Short Form 36.
[a]Mean ± standard deviation (number).
[b]Median (number) [Q1–Q3].

Physical outcomes

Four studies reported on the possible effects on physical function and quality-of-life outcomes, displayed in Table 3. None of the trials found significant differences between groups. However, Wischmeyer et al[46] found trends toward improved handgrip strength at hospital discharge, improved 6-Minute Walk Test, and better Barthel Index at hospital discharge, as well as improved Short Form 36 (SF-36) scores at 6 months in the nutritionally high-risk patients that received a combination of EN and PN. Berger et al[33] observed a trend for less loss of the quadriceps cross-sectional area in those patients receiving SPN.

DISCUSSION

Summary of main results

Our updated systematic review and meta-analysis included 12 RCTs involving 5543 patients. Most trials were small and included heterogenous groups of patients. Although we were unable to statistically aggregate the results, it seemed that uniformly, patients given a combination of EN with PN received greater amounts of macronutrients compared with those who received EN alone. However, this did not translate into any statistically significant effect on the meta-analyzed clinical end points of mortality, hospital or ICU LOS, or duration of mechanical ventilation. Regarding the outcomes "nutrition delivery," "infectious complications," and "physical outcome," the reported data were too heterogeneous to perform meta-analyses. There were no clear findings for infectious complications and glycemic control, especially because the two largest trials (by Casaer et al and Heidegger et al) yielded contradictory results. Our findings may be regarded as hypothesis generating only, but a weak signal was observed indicating that a combination of EN with PN was associated with a trend toward reduced mortality in nutritionally at-risk patients, as demonstrated by the subgroup analysis from Wischmeyer et al and the observed treatment effect in the sensitivity analysis in a subgroup of trials with a nutrition risk assessment. The subgroup analyses of the trials that included patients at some degree of nutrition risk or at risk for malnutrition demonstrated the possibility of a large treatment effect, and the trial by Wischmeyer and colleagues in nutritionally high-risk patients also suggested a trend toward improved physical outcomes with this therapeutic strategy.

Certainty of the evidence

Overall, the risk-of-bias assessment had high variability across all included studies. The random sequence generation, allocation concealment, blinding of personnel, patients, or outcome assessor methods were inconsistent, and the majority of studies either did not perform

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or did not report both key aspects for selection bias adequately. The correctness of using random-effects meta-analyses of this decision was reflected by the existence of high statistical heterogeneity in several meta-analyses. The differences between trials limited the possibility to perform meta-analyses for some outcomes and, as a result, the overall quality of the available evidence. Finally, a lack of information precluded us from providing an informed judgement in several cases. Corresponding authors were contacted, with a low rate of response.

Potential biases in the review process

Our systematic review was performed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and the PRISMA statement for reporting of systematic reviews. Searches and the process of study selection were performed as described above without language restrictions. As a result, we identified no potential sources of bias with regard to the conduct of this systematic review.

Agreements and disagreements with other reviews

In preexisting meta-analyses, the inclusion of different RCTs has led to different results. In this analysis, only adult, severely critically ill patients were included as predefined by the need for mechanical ventilation and high mortality, whereas other meta-analyses have included different patient groups (eg, pediatric patients,[30] ICU patients after elective surgery[30]) and trials without true randomization[26,27,30,31] and have not included the two most recent trials by Ridley et al[32] and Berger et al,[33] necessitating this update. In addition, our meta-analysis focuses not only on mortality as a "hard" outcome but on reports of nutrition and physical outcomes as well.

Shi et al[27] observed fewer respiratory infections in the group receiving EN alone compared with the group receiving a combination of EN with PN (RR = 1.13), as well as a shorter LOS in the hospital (MD, 1.83 days). This group also found no differences between groups regarding hospital mortality, LOS in the ICU, and duration of ventilatory support. Their meta-analysis includes one quasi-randomized trial by Fan et al[47] and a nonrandomized trial by Huang et al[48] but does not include the above-mentioned recent trials[32,33] or two older studies.[40,45]

The Cochrane analysis by Lewis et al[26] found statistically significant differences in favor of a combination of EN with PN compared with EN alone in "mortality at 30 days" ($P = .027$) and wound infections ($P = .011$). No significant differences in pneumonia, urinary tract infection, or bloodstream infection were detected. It must be noted that this analysis did not include the trials by Ridley et al,[32] Berger et al,[33] and Herndon,[44,45] which may explain the differences to our results.

Luo et al[30] included 12 RCTs recruiting a total of 5609 adults and 1440 children in their analysis from 2020. A combination of PN with EN was not associated with the risk of all-cause mortality, respiratory infection, urinary tract infection, ventilatory support, or ICU LOS. A combination of PN with EN was associated with longer hospital stay compared with EN alone. The analysis by this group was largely influenced by three trials: the one by Casaer et al with the early use of PN in both groups as discussed above and two trials that were excluded from our analysis (one because of the patient group being children, by Fivez et al,[49] and the other owing to the inclusion of elective surgery patients, with 0% mortality, by Wu et al[50]). In addition, the nonrandomized trials by Fan[47] and Huang[48] were included in their meta-analysis.

Alsharif et al[31] compared SPN with EN alone in their analysis from 2020, which included five trials. They observed decreased risk of nosocomial infections (three studies; RR = 0.733; $P = .032$) and ICU mortality (four studies; RR = 0.569; $P = .030$) in the SPN group. No significant differences were observed between SPN and EN in the LOS measures, mortality, and duration of mechanical ventilation. It must be noted their meta-analysis did not differentiate between EN+PN and SPN and included fewer trials compared with our current analyses. In addition, the outcome "nosocomial infection" was defined heterogeneously, which is why we abstained from meta-analysis.

Implications for research

Our findings can only be regarded as hypothesis generating. The small sample sizes or small number of trials implies a lack of statistical precision, precluding any firm conclusions. Nevertheless, our findings do raise the question whether a combination of EN with PN in patients at nutrition risk would be beneficial in terms of clinical outcomes.

Of note, some of the included trials did not report nonnutrition energy and therefore may have introduced bias. Future research should therefore cautiously report all macronutrients actually administered to the patients. The inconclusive results of our meta-analysis are likely explained by the heterogenous patient population in trials (for example, the inclusion of a trial of burn patients and a trial of older patients requiring mechanical ventilation) but also by the unselective inclusion regarding the patients' nutrition risk in many of the included individual trials. Therefore, future trials should carefully distinguish between patients with and without high nutrition risk, as the former are expected to benefit the most from adequate nutrition therapy. Patients at high nutrition risk may fall in this category because of preexisting malnutrition, highly invasive surgeries, or the expectation of having a prolonged and potentially complicated ICU stay.

Other explanations include the fact that traditional parameters like mortality, LOS, and duration of ventilation may not represent sensitive end points for the effect of different MNT strategies.[1] These measures may be significantly influenced by other clinical routines and subjective assessment of the treating medical staff. Yet these "traditional" end points were chosen in the included RCTs because they are obviously meaningful, relatively easy to measure, and clearly observable by researchers. Therefore, although these end points are undoubtedly important, they may not adequately capture patients' trajectory after discharge from the ICU or hospital,[51] leading to a more complex meta-analysis. Muscle mass, muscle strength, functional outcomes, and

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quality of life are considered to be more patient-centered and may better capture the MNT-specific treatment effects to be evaluated in future clinical trials.[1] The observed tendency for improvements in functional and patient-reported outcomes in two trials may represent an advantage of a combination of PN with EN, but in both trials, the sample size was too small to draw results other than just hypothesis-generating results.

Implications for clinical practice

Our updated systematic review and meta-analysis revealed that the use of EN+PN as opposed to EN alone improved nutrition delivery in the early phase of critical illness, but this did not translate into an impact on clinical outcomes. Based on the meta-analyzed studies, only nonsignificantly reduced mortality in nutritionally high-risk patients could be detected when EN+PN was provided. Accordingly, a combined approach of EN+PN cannot be recommended with high evidence in all patients, whereas functional outcomes may be more sensitive to detect clinical meaningful effects.

In the subgroup of patients at high nutrition risk, this approach was shown to be effective to increase nutrition delivery. Provided the patient tolerates increased substrate delivery metabolically, this combined approach may represent a promising strategy for patients in whom continued underfeeding with EN alone may result in significant macronutrient deficits.

CONCLUSIONS

A combination of EN with PN improved nutrition intake in the acute phase of critically ill adults and was not inferior regarding the patients' outcomes. Heterogeneity between trials and outcome reporting limited rigorous data synthesis. Our subgroup analysis regarding patients at nutrition risk does raise the question of whether a combination of EN with PN in patients at nutrition risk would be beneficial in terms of clinical outcomes. However, in nutritionally high-risk patients, there may be some benefit to this therapeutic approach that safely maximizes nutrition delivery. Further trials exploring this hypothesis and focusing on muscle mass, strength, and functional performance measures are warranted and currently in preparation, such as the EFFORTcombo trial (ClinicalTrials.gov: NCT 04012333), which will assess the influence of adding high-protein PN to EN in nutritionally high-risk patients and assess functional outcomes in addition to the traditional outcomes measured.[1]

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CONFLICT OF INTEREST

Christian Stoppe has received lecture fees and travel expenses from Fresenius Kabi and consulting fees from Fresenius Kabi and biosyn. Christian Stoppe received a co-funding grant from Baxter Healthcare Corporation to realize an investigator-initiated trial of combined enteral and parenteral nutrition. Gunnar Elke is receiving lecture fees and travel reimbursement by Fresenius Kabi, Baxter Healthcare Corporation, and Nutricia. Gunnar Elke is an advisor for Fresenius Kabi. Aileen Hill and Christian Stoppe have received a grant from Fresenius Kabi unrelated to this analysis. The other authors declare no conflicts of interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results.

FUNDING INFORMATION

None declared.

AUTHOR CONTRIBUTIONS

Aileen Hill and Christian Stoppe equally contributed to the conception and design of the research; Daren K. Heyland and Gunnar Elke contributed to the design of the research; Aileen Hill, Luis A. Ortiz Reyes, Sebastian Wendt, and Elena Laaf contributed to the acquisition and analysis of the data; Aileen Hill, Christian Stoppe, Daren K. Heyland, Gunnar Elke, and Luis A. Ortiz Reyes contributed to the interpretation of the data; and Aileen Hill, Christian Stoppe, and Luis A. Ortiz Reyes drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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REFERENCES

1. Hill A, Heyland DK, Elke G, et al. Meeting nutritional targets of critically ill patients by combined enteral and parenteral nutrition: review and rationale for the EFFORTcombo trial. *Nutr Res Rev*. 2020;33(2):312-320.
2. Lee ZY, Heyland DK. Determination of nutrition risk and status in critically ill patients: what are our considerations? *Nutr Clin Pract*. 2019;34(1):96-111.
3. Preiser J-C, van Zanten ARH, Berger MM, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care*. 2015;19(1):35.
4. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38(1):48-79.
5. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159-211.
6. Elke G, Hartl WH, Kreymann KG, et al. Clinical nutrition in critical care medicine—Guideline of the German Society for Nutritional Medicine (DGEM). *Clin Nutr ESPEN*. 2019;33:220-275.
7. Reintam Blaser A, Starkopf J, Alhazzani W, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med*. 2017;43(3):380-398.
8. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27(5):355-373.

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9. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med*. 2001;29(12):2264-2270.
10. Berger MM, Chiolero RL. Enteral nutrition and cardiovascular failure: from myths to clinical practice. *JPEN J Parenter Enteral Nutr*. 2009;33(6):702-709.
11. Berger MM, Revelly J-P, Cayeux M-C, Chiolero RL. Enteral nutrition in critically ill patients with severe hemodynamic failure after cardiopulmonary bypass. *Clin Nutr*. 2005;24(1):124-132.
12. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr*. 2005;24(4):502-509.
13. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Med*. 2009;35(12):2018-2027.
14. Heyland DK, Schroter-Noppe D, Drover JW, et al. Nutrition support in the critical care setting: current practice in canadian ICUs–opportunities for improvement? *JPEN J Parenter Enteral Nutr*. 2003;27(1):74-83.
15. Heyland D, Cook DJ, Winder B, Brylowski L, Van deMark H, Guyatt G. Enteral nutrition in the critically ill patient: a prospective survey. *Crit Care Med*. 1995;23(6):1055-1060.
16. Adam S, Batson S. A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK. *Intensive Care Med*. 1997;23(3):261-266.
17. McClave SA, Sexton LK, Spain DA, et al. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. *Crit Care Med*. 1999;27(7):1252-1256.
18. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
19. Dhaliwal R, Cahill N, Lemieux M, Heyland DK. The Canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. *Nutr Clin Pract*. 2014;29(1):29-43.
20. Singer P, Berger MM, Van den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. *Clin Nutr*. 2009;28(4):387-400.
21. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med*. 2014;371(18):1673-1684.
22. Reignier J, Boisrame-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet*. 2018;391(10116):133-143.
23. Wernerman J, Christopher KB, Annane D, et al. Metabolic support in the critically ill: a consensus of 19. *Crit Care*. 2019;23(1):318.
24. Berger MM, Pichard C. Parenteral nutrition in the ICU: lessons learned over the past few years. *Nutrition*. 2019;59:188-194.
25. Heidegger C-P, Romand J-A, Treggiari MM, Pichard C. Is it now time to promote mixed enteral and parenteral nutrition for the critically ill patient? *Intensive Care Med*. 2007;33(6):963-969.
26. Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. *Cochrane Database Syst Rev*. 2018;6:CD012276.
27. Shi J, Wei L, Huang R, Liao L. Effect of combined parenteral and enteral nutrition versus enteral nutrition alone for critically ill patients: a systematic review and meta-analysis. *Medicine*. 2018;97(41):e11874.
28. Elke G, van Zanten ARH, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2016;20(1):117.
29. Hill A, Benstoem C, Heyland DK, Stoppe C. Combination of enteral and parenteral nutrition in comparison to enteral nutrition alone–does combination timing matter? *Clin Nutr*. 2019;38(suppl 1):S4.
30. Luo Y, Qian Y. Effect of combined parenteral and enteral nutrition for patients with a critical illness: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2020;99(3):e18778.
31. Alsharif DJ, Alsharif FJ, Aljuraiban GS, Abulmeaty MMA. Effect of supplemental parenteral nutrition versus enteral nutrition alone on clinical outcomes in critically ill adult patients: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2020;12(10):2968.
32. Ridley EJ, Davies AR, Parke R, et al. Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study. *Crit Care*. 2018;22(1):12.
33. Berger MM, Pantet O, Jacquelin-Ravel N, et al. Supplemental parenteral nutrition improves immunity with unchanged carbohydrate and protein metabolism in critically ill patients: the SPN2 randomized tracer study. *Clin Nutr*. 2019;38(5):2408-2416.
34. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res*. 2014;14(1):579.
35. Chen F. Influence of different routes of nutrition on the respiratory muscle strength and outcome of elderly patients in respiratory intensive care unit. *Chin J Clin Nutr*. 2011;19(1):7-11.
36. Chiarelli AG, Ferrarello S, Piccioli A, et al. Total enteral nutrition versus mixed enteral and parenteral nutrition in patients at an intensive care unit. *Minerva Anestesiol*. 1996;62(1-2):1-7.
37. Casaer MP, Hermans G, Wilmer A, Van den Berghe G. Impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients (EPaNIC trial): a study protocol and statistical analysis plan for a randomized controlled trial. *Trials*. 2011;12(1):21.
38. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27(6):1785-1805.
39. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365(6):506-517.
40. Abrishami R, Ahmadi A, Abdollahi M, et al. Comparison the inflammatory effects of early supplemental parenteral nutrition plus enteral nutrition versus enteral nutrition alone in critically ill patients. *Daru*. 2010;18(2):103-106.
41. Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in the critically ill. *Intensive Care Med*. 2000;26(7);893-900.
42. Dunham CM, Frankenfield D, Belzberg H, Wiles C, Cushing B, Grant Z. Gut failure–predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma*. 1994;37(1):30-34.
43. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet*. 2013;381(9864):385-393.
44. Herndon DN, Stein MD, Rutan TC, Abston S, Linares H. Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. *J Trauma*. 1987;27(2):195-204.
45. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehab*. 1989;10(4):309-313.
46. Wischmeyer PE, Hasselmann M, Kummerlen C, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. *Crit Care*. 2017;21(1):142.
47. Fan M, Wang Q, Fang W, et al. Early enteral combined with parenteral nutrition treatment for severe traumatic brain injury: effects on immune function, nutritional status and outcomes. *Chin Med Sci J*. 2016;31(4):213-220.

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48. Huang YC, Yen CE, Cheng CH, Jih KS, Kan MN. Nutritional status of mechanically ventilated critically ill patients: comparison of different types of nutritional support. *Clin Nutr*. 2000;19(2):101-107.
49. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *N Engl J Med*. 2016;374(12):1111-1122.
50. Wu W, Zhong M, Zhu D-M, et al. Effect of early full-calorie nutrition support following esophagectomy: a randomized controlled trial. *JPEN J Parenter Enteral Nutr*. 2017;41(7):1146-1154.
51. Poolman RW, Swiontkowski MF, Fairbank JC, Schemitsch EH, Sprague S, de Vet HC. Outcome instruments: rationale for their use. *J Bone Joint Surg Am*. 2009;91(Suppl 3):41-49.

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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