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CONFERENCE REPORTS AND EXPERT PANEL

Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines

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Abstract

Purpose: To provide evidence-based guidelines for early enteral nutrition (EEN) during critical illness.

Methods: We aimed to compare EEN vs. early parenteral nutrition (PN) and vs. delayed EN. We defined "early" EN as EN started within 48 h independent of type or amount. We listed, a priori, conditions in which EN is often delayed, and performed systematic reviews in 24 such subtopics. If sufficient evidence was available, we performed meta-analyses; if not, we qualitatively summarized the evidence and based our recommendations on expert opinion. We used the GRADE approach for guideline development. The final recommendations were compiled via Delphi rounds.

Results: We formulated 17 recommendations favouring initiation of EEN and seven recommendations favouring delaying EN. We performed five meta-analyses: in unselected critically ill patients, and specifically in traumatic brain injury, severe acute pancreatitis, gastrointestinal (GI) surgery and abdominal trauma. EEN reduced infectious complications in unselected critically ill patients, in patients with severe acute pancreatitis, and after GI surgery. We did not detect any evidence of superiority for early PN or delayed EN over EEN. All recommendations are weak because of the low quality of evidence, with several based only on expert opinion.

Conclusions: We suggest using EEN in the majority of critically ill under certain precautions. In the absence of evidence, we suggest delaying EN in critically ill patients with uncontrolled shock, uncontrolled hypoxaemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate >500 ml/6 h, bowel ischaemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access.

Keywords: Abdominal problems, Parenteral nutrition, Contraindications, GI symptoms, Early enteral nutrition, Delay of enteral nutrition

Introduction

Existing guidelines recommend initiating enteral nutrition (EN) within the first 24–48 h after intensive care unit (ICU) admission if patients are unable to eat, not clearly defining reasons to delay EN [1–3]. The present guideline is issued by the Working Group on Gastrointestinal Function within the Metabolism, Endocrinology and Nutrition (MEN) Section of the European Society

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Take-home message: The administration of early EN appears to reduce infections and should be used for the majority of critically ill patients. However, there are certain situations when we recommend EN be delayed.

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Table 1 General principles and precautions for using EEN in critically ill patients at risk of intolerance

Starting and continuing EEN	Start EN at a slow rate (10–20 ml/h) while carefully monitoring abdominal/gastrointestinal symptoms
	Increase EN slowly once previous symptoms are resolving and no new symptoms occur
	Do not increase EN in cases of intolerance or new symptoms, such as pain, abdominal distension or increasing intra-abdominal pressure. In these circumstances EN should be either continued at a slow rate or ceased depending on the severity of symptoms and suspected underlying sinister pathology (e.g. mesenteric ischaemia)
Energy target during EEN	Do not aim to cover full energy target with EEN. The optimal energy and protein target in the early phase of acute critical illness is not known. EEN that exceeds actual energy expenditure appears harmful and should be avoided [4, 5], whereas hypocaloric EEN may be safe [6–8]
Monitoring and protocolised management of GI dysfunction during EEN	In case of gastric retention without other new abdominal symptoms use prokinetics and/or postpyloric feeding in a protocolised way [9]
	During introduction and increasing the rate of EN, measurement of intra-abdominal pressure (IAP) provides an additional numeric value to detect negative dynamics of IAP during EN in patients with severe abdominal pathology, hypoperfusion or fluid overload
Individualized approach	For patients with diminished consciousness and inadequate swallowing, precautions to prevent aspiration of gastric contents may be useful, including considering postpyloric feeding
	Premorbid health and course of the acute illness may differ between patients with similar diagnose; therefore an individual approach should always be applied

of Intensive Care Medicine (ESICM) and is endorsed by ESICM. Our objective was to provide evidence-based guidelines for early enteral nutrition (EEN) in critically ill patients, focusing on specific clinical conditions frequently associated with delayed EN. Caloric and protein requirements, time to reach targets, type and route of EN, and timing of supplemental or full parenteral nutrition (PN) were not addressed. A full version of the introduction with references is available in Supplement 1.

Methods

A full version of methods with references is available in Supplement 1.

We performed a systematic review of "early" EN (EEN) vs. early parenteral nutrition (PN) and EEN vs. delayed EN in adult critically ill patients. After critical appraisal of identified studies and in accordance with current guidelines [1–3], we defined EEN as EN started within 48 h of admission independent of the type or amount.

Thereafter, we predefined conditions in which EN is frequently delayed and performed a systematic review for each of these questions.

If randomised controlled trials (RCT) were available, we gave an evidence-based recommendation; if not, our recommendations were based on expert opinion (very low quality evidence), as all observational studies evaluating EEN are intrinsically biased, because patients who are less severely ill are more likely to receive and tolerate EEN.

General considerations

We focussed on specific conditions in which EN is frequently delayed and tolerance of EN might be impaired. Therefore, all our recommendations are based on general principles and precaution measures outlined in Table 1 [4–9]. All study questions and recommendations refer to adult critically ill patients.

Results

All recommendations with the final agreed results are presented in Table 2.

A flow chart with evidence identification process (Supplement 2), number of identified abstracts and assessed full texts for each study question (Supplement 3), Pubmed search formulas (Supplement 4), evidence tables for each question with respective references (Supplement 5), evidence profiles for questions with meta-analyses (Table 3), evidence profiles for additional meta-analyses for Question 1 and 11 (Supplement 6), Forest plots for meta-analyses (Figs. 1, 2 and Supplement 7) are provided.

Question 1: Should we use EEN in critically ill adult patients?

The methodology is described in Supplement 1.

Table 2 Recommendations

Recommendation	Agreement (%)	Comments
1. We suggest using EEN in critically ill adult patients rather than early PN (conditional recommendation based on low quality evidence = Grade 2C) or delaying EN (conditional recommendation based on low quality evidence = Grade 2C)	100	
2. We suggest delaying EN if shock is uncontrolled and haemodynamic and tissue perfusion goals are not reached, but start low dose EN as soon as shock is controlled with fluids and vasopressors/inotropes (conditional recommendation based on expert opinion = Grade 2D)	91.4	Concern regards applying EN when very high doses of vasopressors (e.g. noradrenalin >1 μg/kg/min) are required and hyperlactatemia is persisting or other signs of end organ hypoperfusion are present
3. We suggest delaying EN in case of uncontrolled life-threatening hypoxaemia, hypercapnia or acidosis, but using EEN in patients with stable hypoxaemia, and compensated or permissive hypercapnia and acidosis (conditional recommendation based on expert opinion = Grade 2D)	100	
4. We suggest that EN should not be delayed solely because of the concomitant use of neuromuscular blocking agents (conditional recommendation based on expert opinion = Grade 2D)	91.4	Concern regards very seldom patients in whom continuous infusion of neuromuscular blocking agents is needed, because these patients are in a very critical situation
5. We suggest starting low dose EEN in patients receiving therapeutic hypothermia and increase the dose after rewarming (conditional recommendation based on expert opinion = Grade 2D)	100	
6. We suggest using EEN in adult patients receiving extracorporeal membrane oxygenation (conditional recommendation based on expert opinion = Grade 2D)	100	
7. We suggest that EN should not be delayed solely because of prone positioning (conditional recommendation based on expert opinion = Grade 2D).	91.4	Concern regards tolerance of EN
8. We suggest using EEN in critically ill adult patients with traumatic brain injury (conditional recommendation based on expert opinion = Grade 2D)	95.7	No agreement regards strength of recommendation
9. We suggest using EEN in critically ill adult patients with stroke (ischaemic or haemorrhagic) (conditional recommendation based on expert opinion = Grade 2D)	100	
10. We suggest using EEN in critically ill adult patients with spinal cord injury (conditional recommendation based on expert opinion = Grade 2D)	100	
11. We suggest using EEN in critically ill adult patients with severe acute pancreatitis (conditional recommendation based on low quality evidence = Grade 2C)	100	
12. We suggest using EEN in critically ill adult patients after gastrointestinal surgery (conditional recommendation based on low quality evidence = Grade 2C)	100	
13. We suggest using EEN in critically ill adult patients after abdominal aortic surgery (conditional recommendation based on expert opinion = Grade 2D)	100	
14. We suggest using EEN in critically ill adult patients with abdominal trauma after the continuity of the GI tract is confirmed/restored (conditional recommendation based on expert opinion = Grade 2D)	100	Adequate gut perfusion needs to be confirmed
15. We suggest delaying EN in critically ill adult patients with overt bowel ischaemia (conditional recommendation based on expert opinion = Grade 2D)	100	

Table 2 continued

Recommendation	Agreement (%)	Comments
16. We suggest delaying EN in critically ill adult patients with high-output intestinal fistula if reliable feeding access distal to the fistula is not achievable (conditional recommendation based on expert opinion = Grade 2D)	100	
17. We suggest using EEN in critically ill adult patients with an open abdomen (conditional recommendation based on expert opinion = Grade 2D)	100	
18a. We suggest using EEN in patients with intra-abdominal hypertension without abdominal compartment syndrome, but consider temporary reduction or discontinuation of EN when intra-abdominal pressure values further increase under EN (conditional recommendation based on expert opinion = Grade 2D)	87.1	Concern regards impaired gut perfusion and tolerance of EN. Monitoring trend of IAH and tolerance of EN are essential
18b. We suggest delaying EN in critically ill adult patients with abdominal compartment syndrome (conditional recommendation based on expert opinion = Grade 2D)	100	
19. We suggest delaying EN in patients with active upper GI bleeding, and starting EN when the bleeding has stopped and no signs of rebleeding are observed (conditional recommendation based on expert opinion = Grade 2D)	100	
20. We suggest starting low dose enteral nutrition when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy (conditional recommendation based on expert opinion = Grade 2D)	100	
21. We suggest delaying EN in critically ill adult patients if gastric aspirate volume is above 500 ml/6 h (conditional recommendation based on expert opinion = Grade 2D	91.4	Single large gastric aspirate volume should trigger administration of prokinetics and reassessment, but not prolonged withholding of EN
22. We suggest using EEN in critically ill adult patients regardless of the presence of bowel sounds unless bowel ischaemia or obstruction is suspected (conditional recommendation based on expert opinion = Grade 2D)	100	
23. We suggest using EEN in critically ill adult patients presenting with diarrhoea (conditional recommendation based on expert opinion = Grade 2D)	95.7	Uncertainty regards volume and persistence of diarrhoea

Response rate was 100% in both Delphi rounds (all co-authors responded, methodologist did not participate). Agreement is calculated as percentage of "agree" answers from total

Table 3 Evidence profiles for the questions where meta-analyses were performed

Question 1												
Question 1A	**Early EN vs early PN in unselected critically ill population (identified during primary search using key words block on „critical illness")**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EEN**	**EPN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
7	randomised trials	not serious[1]	not serious[2]	not serious	serious[3]	none	431/1335 (32.3%)	431/1337 (32.2%)	**RR 0.95** (0.76 to 1.19)	**16 fewer per 1,000** (from 61 more to 77 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any Infections												
7	randomised trials	serious[4]	serious[5]	not serious	not serious	none	283/1364 (20.7%)	335/1365 (24.5%)	**RR 0.55** (0.35 to 0.86)	**110 fewer per 1,000** (from 34 fewer to 160 fewer)	⊕⊕◯◯ LOW	CRITICAL

Comments:
1. Although the randomization method was inappropriate or unclear in four RCTs out of five, we did not downgrade for risk of bias because the overall results did not change after excluding high risk of bias trials from the analysis, it is unlikely that risk of bias affected the mortality estimate.
2. We did not downgrade for inconsistency (I^2 = 9%)
3. We downgraded for imprecision by one level because the CI included significant benefit and harms (076, 1.19)
4. We downgraded for risk of bias by one level, most RCTs were non-blinded and had unclear or inappropriate methods of randomization
5. We downgraded for inconsistency by one level due to significant statistical heterogeneity (I^2 = 65%)

Question 1B	**Early EN vs delayed EN in unselected critically ill population (identified during primary search using key words block on „critical illness")**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early nutrition**	**Delayed nutrition**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
12	randomised trials	serious[1]	not serious[2]	not serious	serious[3]	none	38/336 (11.3%)	54/326 (16.6%)	**RR 0.76** (0.52 to 1.11)	**40 fewer per 1,000** (from 18 more to 80 fewer)	⊕⊕◯◯ LOW	CRITICAL
Any Infections												
11	randomised trials	serious[1]	not serious[4]	not serious	serious[5]	none	65/299 (21.7%)	103/298 (34.6%)	**RR 0.64** (0.46 to 0.90)	**124 fewer per 1,000** (from 35 fewer to 187 fewer)	⊕⊕◯◯ LOW	CRITICAL

Comments:
1. We downgraded by one level for risk of bias, all RCTs had either inappropriate or unclear randomization methods
2. I^2 = 0%
3. We downgraded by one level for imprecision, the CI crosses the line of unity.
4. We did not downgrade for inconsistency, the I^2 = 25%
5. We downgraded the quality of evidence by one level for imprecision, the number of events was small, and the CI included small benefit

Question 1A: Should we use EEN rather than early PN?

Eight trials fulfilled the criteria and were included in meta-analyses (Supplement 5, Table 1A). Results are presented in Fig. 1.

For *mortality*, we included seven RCTs (2686 patients). EEN did not reduce mortality compared to early PN (RR 0.95; 95% CI 0.76–1.19; $P = 0.64$; $I^2 = 9\%$). The certainty of evidence was **moderate**. We rated down for imprecision (Table 3).

For *infection*, we included seven RCTs (2729 patients). EEN reduced the risk of infections compared to early PN (RR 0.55; 95% CI 0.35–0.86; $P = 0.009$; $I^2 = 65\%$). The certainty of evidence was **low**. We rated down for risk of bias and inconsistency (Table 3).

Adding 11 additional studies identified during searches for questions in specified patient groups did not significantly change our results (included studies are presented in Supplement 5, Table 1C; evidence profiles in Supplement 6 and Forest plots in Supplement 7, Fig. 3).

Table 3 continued

Question 8	Traumatic brain injury											
Question 8A	**Early EN vs early PN**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EEN**	**EPN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
3	randomised trials	not serious	not serious	not serious	very serious[1]	none	9/61 (14.8%)	4/55 (7.3%)	**RR 1.91** (0.59 to 6.18)	**66 more per 1,000** (from 30 fewer to 377 more)	⨁⨁◯◯ LOW	CRITICAL
Pneumonia												
3	randomised trials	serious[2]	not serious	not serious	very serious[3]	none	27/61 (44.3%)	20/55 (36.4%)	**RR 1.23** (0.79 to 1.90)	**84 more per 1,000** (from 76 fewer to 327 more)	⨁◯◯◯ VERY LOW	CRITICAL

Comments:
1. We downgraded the quality of evidence by two levels for serious imprecision, the CI included extreme benefit and harm
2. We downgraded the quality of evidence for risk of bias by one level
3. We downgraded the quality of evidence by two levels for imprecision, the CI is very wide

Question 8B	**Early EN vs delayed EN**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EEN**	**DEN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
2	randomised trials	not serious	not serious	not serious	very serious[1]	none	4/46 (8.7%)	6/40 (15.0%)	**RR 0.66** (0.18 to 2.45)	**51 fewer per 1,000** (from 123 fewer to 218 more)	⨁⨁◯◯ LOW	CRITICAL
Pneumonia												
3	randomised trials	serious[2]	not serious	not serious	very serious [3]	none	21/63 (33.3%)	22/55 (40.0%)	**RR 0.86** (0.55 to 1.35)	**56 fewer per 1,000** (from 140 more to 180 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Comments:
1. We downgraded the quality of evidence by two levels for imprecision, the number of events is very low
2. We downgraded the quality of evidence for risk of bias by one level, studies were non-blinded
3. We downgraded the quality of evidence by two levels for imprecision, the CI is extremely wide contains significant substantial benefit and harm

Question 1B: Should we use EEN rather than delay nutritional intake?

Fourteen studies fulfilled the criteria and were included in the meta-analysis (Supplement 5, Table 1B). Results of the meta-analyses on EEN vs. delayed nutritional intake (including delayed EN, oral diet or PN) are presented in Fig. 2.

For *mortality*, we included 12 RCTs (662 patients). EEN did not reduce mortality compared to delayed nutritional intake (RR 0.76; 95% CI 0.52–1.11; $P = 0.149$; $I^2 = 0\%$).

For *infection*, we included 11 RCTs (597 patients). EEN reduced risk of infection compared to delayed EN (RR 0.64; 95% CI 0.46–0.90; $P = 0.010$; $I^2 = 25\%$).

Table 3 continued

Question 11	Severe acute pancreatitis											
Question 11A	**SAP (as stated by the authors). Early (early as defined by the authors) EN vs. PN**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EN**	**PN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
5	randomised trials	not serious	not serious	not serious	very serious[1]	none	14/136 (10.3%)	33/147 (22.4%)	**RR 0.57** (0.23 to 1.38)	**97 fewer per 1,000** (from 85 more to 173 fewer)	⨁⨁◯◯ LOW	CRITICAL
Infections												
5	randomised trials	not serious	serious[2]	not serious	serious[3]	none	37/136 (27.2%)	81/147 (55.1%)	**RR 0.48** (0.23 to 0.98)	**287 fewer per 1,000** (from 11 fewer to 424 fewer)	⨁⨁◯◯ LOW	CRITICAL
Pancreatic Infections												
4	randomised trials	serious[4]	not serious	not serious	serious[5]	none	18/111 (16.2%)	57/122 (46.7%)	**RR 0.33** (0.21 to 0.52)	**313 fewer per 1,000** (from 224 fewer to 369 fewer)	⨁⨁◯◯ LOW	CRITICAL

Comments:
1. We downgraded the quality of evidence by two levels for imprecision
2. We downgraded the quality of evidence for inconsistency by one level, the I2 = 76%
3. We downgraded the quality of evidence by one level for imprecision, the number of events was small and the CI includes small benefit
4. We downgraded the quality of evidence for risk of bias, trials were not blinded
5. We downgraded the quality of evidence for imprecision, the number of events is small

Question 12												
Question 12A	**Emergency GI surgery. Early EN vs delayed EN.**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EEN**	**DEN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
3	randomised trials	not serious	not serious	not serious	very serious[1]	none	19/171 (11.1%)	24/172 (14.0%)	**RR 0.80** (0.46 to 1.40)	**28 fewer per 1,000** (from 56 more to 75 fewer)	⨁⨁◯◯ LOW	CRITICAL
Infections												
3	randomised trials	serious[2]	not serious	not serious	serious[3]	none	27/171 (15.8%)	46/172 (26.7%)	**RR 0.61** (0.40 to 0.93)	**110 fewer per 1,000** (from 27 fewer to 163 fewer)	⨁⨁◯◯ LOW	CRITICAL

Comments:
1. We downgraded by two levels for serious imprecision, the CI is very wide and includes substantial benefit and harm
2. All included trials were at high risk of bias
3. We downgraded by one level for imprecision, the number of events was low

The certainty of evidence was **low**. We rated down for risk of bias and imprecision (Table 3).

In one study it was not possible to determine whether early PN was also used in some patients in the EEN group [10]. Adding eight additional studies identified via specific searches did not significantly change the results (included studies are presented in Supplement 5, Table 1D; evidence profiles in Supplement 6 and Forest plots in Supplement 7, Fig. 4).

Recommendation 1. We suggest using EEN in critically ill adult patients rather than early PN (Grade 2C) or delaying EN (Grade 2C).

Question 2: Should we delay EN in patients with shock receiving vasopressors or inotropes?

No RCTs were retrieved. We identified and analysed four prospective cohort studies, four case series/retrospective cohort studies and two reviews (Supplement 5, Table 2).

Table 3 continued

Question 12B	Elective GI surgery. Early EN vs delayed EN											
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EEN	DEN	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	not serious	not serious	not serious	very serious[1]	none	7/176 (4.0%)	7/170 (4.1%)	**RR 0.83** (0.25 to 2.81)	**1 fewer per 1,000** (from 26 fewer to 65 more)	⨁⨁◯◯ LOW	CRITICAL
Infections												
6	randomised trials	serious[2]	not serious[3]	not serious	serious[4]	none	33/218 (15.1%)	65/214 (30.4%)	**RR 0.43** (0.23 to 0.82)	**173 fewer per 1,000** (from 55 fewer to 234 fewer)	⨁⨁◯◯ LOW	CRITICAL
Anastomotic leak												
5	randomised trials	not serious	not serious	not serious	very serious[5]	none	8/204 (3.9%)	20/200 (10.0%)	**RR 0.43** (0.20 to 0.93)	**57 fewer per 1,000** (from 7 fewer to 80 fewer)	⨁⨁◯◯ LOW	CRITICAL

Comments:
1. The CI is extremely wide and number of events is very low, therefore, we downgraded by two levels for imprecision
2. All studies were non-blinded, therefore, we downgraded by one level for risk of bias
3. I2=46% but we did not consider this as a substantial heterogeneity
4. The number of events is small and the CI included both substantial and small benefit
5. We downgraded the quality of evidence by two levels for serious imprecision

Question 12C	Elective GI surgery. Early EN vs early PN											
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EEN	EPN	Relative (95% CI)	Absolute (95% CI)		
Pneumonia												
2	randomised trials	serious[1]	not serious	not serious	serious[2]	none	13/220 (5.9%)	22/220 (10.0%)	**RR 0.59** (0.31 to 1.14)	**41 fewer per 1,000** (from 14 more to 69 fewer)	⨁⨁◯◯ LOW	CRITICAL
Anastomotic leak												
2	randomised trials	not serious	serious[3]	not serious	serious[4]	none	8/220 (3.6%)	19/220 (8.6%)	**RR 0.42** (0.19 to 0.95)	**50 fewer per 1,000** (from 4 fewer to 70 fewer)	⨁⨁◯◯ LOW	CRITICAL

Comments:
1. both trials were non-blinded, we downgraded for risk of bias
2. We downgraded the quality of evidence for imprecision by one level, the CI included the unity line
3. I2=63%
4. We downgraded for imprecision, the number of events was very small and the results were sensitive to pooling method

There is concern that EN in shock further jeopardizes the already impaired splanchnic perfusion. Non-occlusive bowel necrosis or non-occlusive mesenteric ischaemia (NOMI) has been reported in fewer than 1% of patients [11, 12], without evidence for causal relationship between shock, vasopressors, EN and NOMI [11–14]. In a large observational study, EEN (<48 h) in patients with 'stable' haemodynamics after fluid resuscitation, whilst receiving at least one vasopressor, was associated with reduced mortality compared to late EN (>48 h) [15]. These results suggest that the use of concomitant vasopressors (especially with stable or decreasing doses) should not preclude a trial of EN, despite a high prevalence of feeding intolerance [16]. In very unstable patients, EN may not have priority and potential positive effects of EN are unlikely to help improve instability. Persisting lactic acidosis may help identify uncontrolled shock.

Table 3 continued

Question 14	Abdominal trauma											
Question 14A	**Early EN vs early PN**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EEN**	**EPN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
2	randomised trials	serious[1]	not serious	not serious	very serious[2]	none	2/74 (2.7%)	4/68 (5.9%)	**RR 0.49** (0.09 to 2.69)	**30 fewer per 1,000** (from 54 fewer to 99 more)	⊕◯◯◯ VERY LOW	CRITICAL
Infections												
4	randomised trials	serious[3]	serious[4]	not serious	serious[5]	none	22/113 (19.5%)	34/106 (32.1%)	**RR 0.59** (0.24 to 1.42)	**132 fewer per 1,000** (from 135 more to 244 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Comments:
1. We downgraded by one level for risk of bias, the two trials we at high risk of bias
2. We downgraded by two levels for very serious imprecision, the number of events is very low and the CI is extremely wide
3. We downgraded by one level for risk of bias
4. We downgraded by one level for inconsistency, I2= 59%
5. We downgraded by one level for imprecision, the CI included significant benefit and harm, and the number of events was small

Question 14B	**Abdominal trauma. Early EN vs delayed EN.**											
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EEN**	**DEN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
2	randomised trials	serious[1]	not serious	not serious	very serious[2]	none	3/51 (5.9%)	4/50 (8.0%)	**RR 0.74** (0.18 to 3.11)	**21 fewer per 1,000** (from 66 fewer to 169 more)	⊕◯◯◯ VERY LOW	CRITICAL
Infections												
2	randomised trials	serious[1]	very serious[3]	not serious	very serious[2]	none	11/51 (21.6%)	13/50 (26.0%)	**RR 0.83** (0.41 to 1.70)	**44 fewer per 1,000** (from 153 fewer to 182 more)	⊕◯◯◯ VERY LOW	CRITICAL

Comments:
1. We downgraded by one level for risk of bias, the two RCTs had unclear randomization methods
2. We downgraded by two levels for serious imprecision, the CI is very wide including a substantial benefit and harm
3. I^2=81%

EN enteral nutrition, *PN* parenteral nutrition, *CI* confidence interval, *RR* risk ratio, *GI* gastrointestinal

Recommendation 2. We suggest delaying EN if shock is uncontrolled and haemodynamic and tissue perfusion goals are not reached, but start low dose EN as soon as shock is controlled with fluids and vasopressors/ inotropes (Grade 2D).

Question 3:

Should we delay EN in patients with:

A. **Hypoxaemia;**
B. **Hypercapnia;**
C. **Acidosis?**

We found no direct evidence on these subquestions in the literature, and RCTs in this population are unlikely to become available.

The rationale to withhold EN in patients with hypoxaemia, hypercapnia and acidosis is to limit oxygen consumption and CO_2 production. However, the process of starving mobilises endogenous stores and is energy-consuming [17]. Acidosis may represent persistent shock and possibly contribute to gut dysfunction. Identifying and treating the cause of shock has priority over the initiation of EN. Similarly, in uncontrolled life-threatening hypoxaemia and hypercapnia, EN should be delayed until the symptoms are resolving.

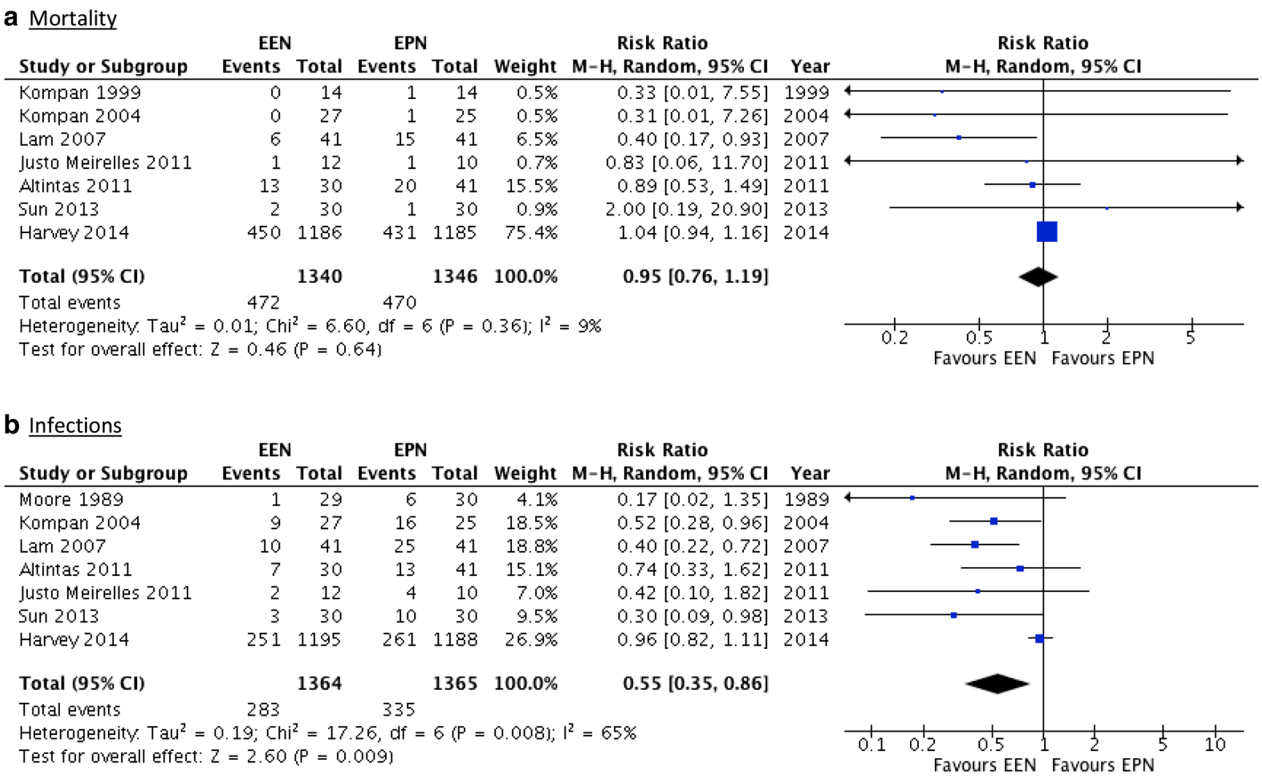

Fig. 1 Forest plots (**a** mortality; **b** infections) Question 1A: early EN (EEN) vs. early PN (EPN) in unselected critically ill patients

In patients with acute lung injury, an RCT comparing trophic to full EN for up to 6 days was associated with less gastrointestinal intolerance when compared to full EN, without affecting ventilator-free days, infectious complications, physical function, or survival [7, 18]. There are no data suggesting EN in patients with chronic, subacute, compensated or permissive hypercapnia is unsafe or not feasible.

Recommendation 3. We suggest delaying EN in case of uncontrolled life-threatening hypoxaemia, hypercapnia or acidosis, but using EEN in patients with stable hypoxaemia, and compensated or permissive hypercapnia and acidosis (Grade 2D).

Question 4: Should we delay EN in patients receiving neuromuscular blocking agents?

One prospective study was identified (Supplement 5, Table 4), reporting similar gastric emptying as measured by gastric residual volume (GRV) in sedated patients with or without concomitant use of neuromuscular blocking agents [19]. The critical condition necessitating the use of neuromuscular blocking agents always needs to be considered, but these agents per se should not preclude EN. Analgosedation is known to slow gastric emptying [20]. Increased rate of EN intolerance is expected in deeply sedated patients with/without concomitant use of neuromuscular blocking agents.

Recommendation 4. We suggest that EN should not be delayed solely because of the concomitant use of neuromuscular blocking agents (Grade 2D).

Question 5: Should we delay EN in patients receiving therapeutic hypothermia?

One case series study addressing EN during therapeutic hypothermia was identified [21] (Supplement 5, Table 5).

During therapeutic hypothermia, energy metabolism might be markedly reduced [22, 23] when shivering is prevented. The rationale to withhold EN during therapeutic hypothermia is based on the presumed decrease in gut motility due to hypothermia [24, 25] and required analgosedation [20]. It has been suggested that EN could be successfully administered to

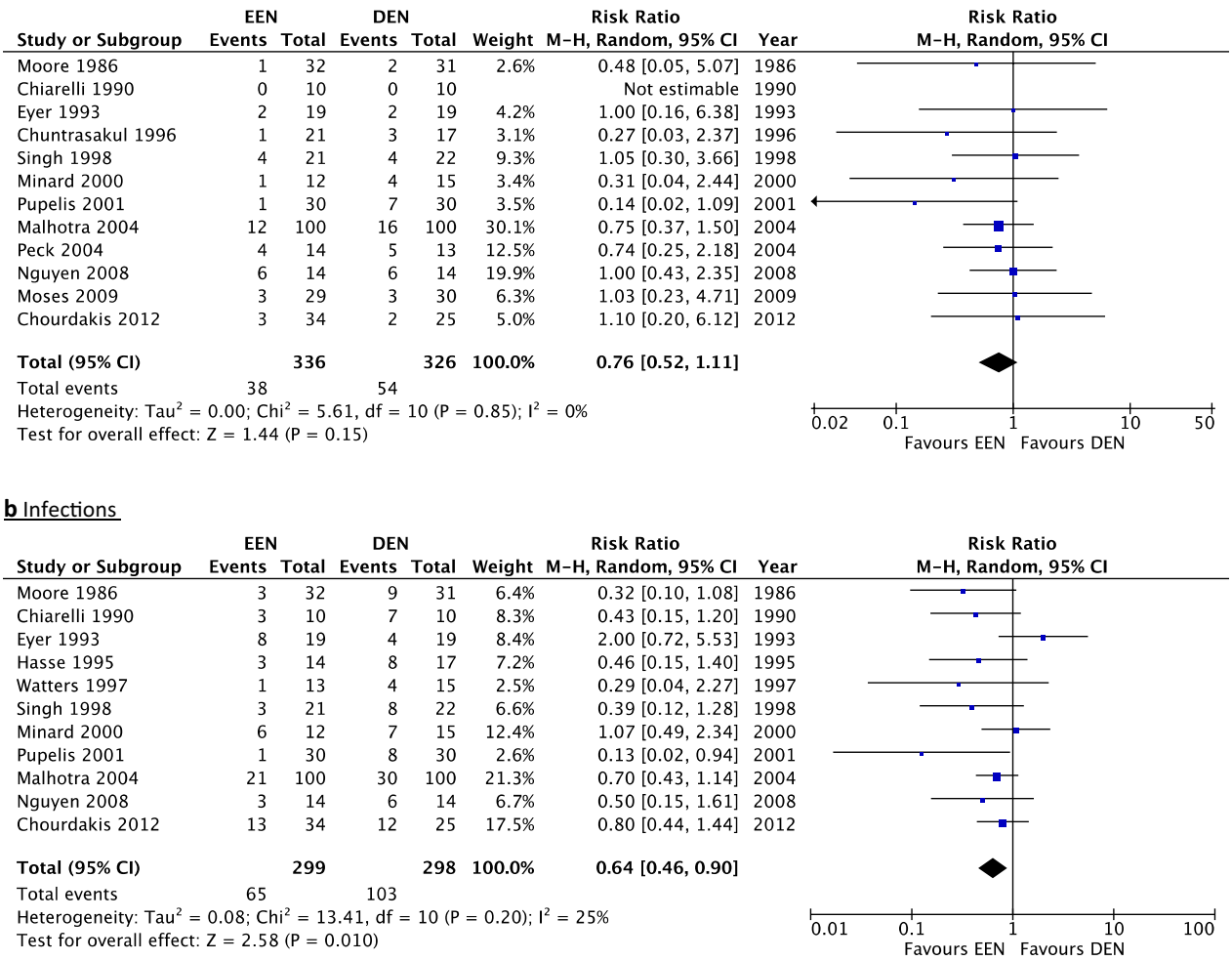

Fig. 2 Forest plots (**a** mortality; **b** infections) Question 1B: early EN (EEN) vs. delayed EN (DEN) in unselected critically ill patients

these patients [21]. Tolerance to enteral feeding was impaired during hypothermia, but improved during rewarming [21].

Recommendation 5. We suggest starting low dose EEN in patients receiving therapeutic hypothermia and increase the dose after rewarming (Grade 2D).

Question 6: Should we delay EN in patients receiving extracorporeal membrane oxygenation (ECMO)?

No RCTs and no prospective cohort studies were identified. Four case series in adult patients with ECMO were assessed (Supplement 5, Table 6), suggesting that EN is feasible during ECMO.

Recommendation 6. We suggest using EEN in patients receiving ECMO (Grade 2D).

Question 7: Should we delay EN during prone position?

One prospective cross-over, one cohort and three case series studies were identified (Supplement 5, Table 7).

Data on tolerance of EN in prone position are controversial. Observational studies found similar GRVs in prone and supine position [26], whereas poor feeding tolerance was improved with semi-recumbent position during supine periods and prokinetics [27, 28]. Although no RCTs on EN tolerance during prone position are available, reported studies do not support withholding EN in

prone position. Gastric emptying seems not to be significantly influenced by prone position and adverse events in most studies not increased.

Recommendation 7. We suggest that EN should not be delayed solely because of prone positioning (Grade 2D).
Remark: We suggest considering early use of prokinetics followed by post-pyloric feeding in case of persisting gastric retention.

Question 8: Should we delay EN in patients with traumatic brain injury?

We identified a Cochrane review with two updates and one recent meta-analysis, comparing early vs. late feeding, independent on the route of nutrition (EN or PN) (Supplement 5, Table 8C). We identified three RCTs comparing EEN vs. early PN, three RCTs comparing EEN vs. delayed EN (one with restricted randomisation), and one RCT comparing early PN vs. delayed EN (Supplement 5, Table 8A).

Question 8A: EEN vs. early PN

Three RCTs (116 patients) were included. EEN compared to early PN in patients with traumatic brain injury did not affect mortality (RR 1.91; 95% CI 0.59–6.18; $P = 0.279$; $I^2 = 0\%$) or the risk of pneumonia (RR 1.23; 95% CI 0.79–1.90; $P = 0.36$; $I^2 = 0\%$). The certainty of evidence for mortality outcome was **low**, for pneumonia it was **very low**. We rated down for risk of bias and imprecision (Table 3). Supplement 7, Fig. 5.

Question 8B: EEN vs. delayed EN

For *mortality*, two RCTs (86 patients) were included. EEN did not affect mortality compared to delayed EN (RR 0.66; 95% CI 0.18–2.45; $P = 0.53$; $I^2 = 0\%$). The certainty of evidence was **low**. We rated down for imprecision (Table 3).

For *pneumonia*, three RCTs (118 patients) were included. EEN did not affect the risk of pneumonia compared to delayed EN (RR 0.86; 95% CI 0.55–1.35; $P = 0.51$; $I^2 = 0\%$). The certainty of evidence was **very low**. We rated down for risk of bias and imprecision (Table 3). Supplement 7, Fig. 6.

In addition to RCTs, five cohort studies addressing this question were identified (Supplement 5, Table 8B).

Existing evidence did not allow determining or excluding any benefit or harm of EEN, therefore our recommendation is based on expert opinion.

Recommendation 8. We suggest using EEN in patients with traumatic brain injury (Grade 2D).

Question 9: Should we delay EN in patients with stroke (haemorrhagic or ischaemic)?

We identified two RCTs in patients with ischaemic stroke and one retrospective study in patients with hypertensive intracerebral haemorrhage (Supplement 5, Tables 9A, B).

One small RCT compared early vs. delayed EN and reported amelioration of cell-mediated immunity [29]; however, both groups received PN to meet caloric targets from day 1. A large RCT compared EEN ("as soon as possible") to no nutrition within 7 days and reported a trend towards reduction of long-term mortality (6 months) with EN, with an increased risk of poor neurologic outcome in survivors [30]. An observational study reported reduction in infectious complications with EEN vs. delayed EN [31].

Recommendation 9. We suggest using EEN in patients with stroke (ischaemic or haemorrhagic) (Grade 2D).

Question 10: Should we delay EN in patients with spinal cord injury?

One RCT addressed EEN (<72 h) vs. delayed EN in cervical spinal injury [32]. No differences in outcome variables were identified. One retrospective cohort study addressed safety of EN early after spinal cord injury and reported no major complications [33] (Supplement 5, Tables 10A, B).

Recommendation 10. We suggest using EEN in patients with spinal cord injury (Grade 2D).

Question 11: Should we delay EN in patients with severe acute pancreatitis (SAP)?

We identified five systematic reviews with meta-analyses comparing EN to PN while not considering timing (Supplement 5, Table 11B). All meta-analyses concluded that EN was beneficial in reducing infections and three reported reduced mortality [3, 34, 35].

We identified five RCTs addressing EEN ("early" as defined by the authors) vs. early PN in SAP whereas only two studies defined "early" as <48 h. Three further RCTs addressed EEN vs. early PN and one RCT EEN vs. delayed EN in "predicted SAP". Two RCTs addressing acute pancreatitis independent of severity and one RCT

studying mixed patients undergoing abdominal surgery were not included. Supplement 5, Table 11A.

We performed three separate meta-analyses all comparing EEN vs. early PN: (A) SAP and "early" as defined by the authors of the original study; (B) predicted SAP and "early" as defined by the authors of the original study; (C) predicted SAP and early defined as <48 h.

Question 11A: SAP (as stated by the authors). Early ("early" as defined by the authors) EN vs. PN

For *mortality* we included five RCTs (283 patients). EEN did not reduce the risk of death compared to PN (RR 0.57; 95% CI 0.23–1.38; $P = 0.21$; $I^2 = 35.1\%$). The certainty of evidence was **low**. We rated down for imprecision (Table 3).

For *any infections* we included five RCTs (283 patients). EEN reduced the risk of infections compared to PN (RR 0.48; 95% CI 0.23–0.98; $P = 0.045$; $I^2 = 76\%$). The certainty of evidence was **low**. We rated down for inconsistency and imprecision (Table 3).

For *pancreatic infections* we included four RCTs (233 patients). EEN reduced the risk of pancreatic infections compared to PN (RR 0.33; 95% CI 0.21–0.52; $P < 0.0001$; $I^2 = 0\%$) The certainty of evidence was **low**. We rated down for risk of bias and imprecision (Table 3). Supplement 7, Fig. 7.

Question 11B: Predicted SAP. Early ("early" as defined by the authors) EN vs. PN

For *mortality* we included eight RCTs (417 patients). EEN did not reduce the risk of death compared to PN (RR 0.50; 95% CI 0.22–1.13; $P = 0.09$; $I^2 = 38\%$). The certainty of evidence was **low**. We rated down for imprecision (Supplement 6).

For *any infections* we included eight RCTs (417 patients). EEN reduced the risk of infections compared to PN (RR 0.53; 95% CI 0.30–0.91; $P = 0.023$; $I^2 = 63.5\%$). The certainty of evidence was **low**. We rated down for risk of bias and inconsistency (Supplement 6).

For *pancreatic infections* we included five RCTs (202 patients). The use of EEN reduced the risk of pancreatic infections compared to PN (RR 0.35; 95% CI 0.24–0.52; $P < 0.0001$; $I^2 = 0\%$). The certainty of evidence was **low**. We rated down for risk of bias and imprecision (Supplement 6). Supplement 7, Fig. 8.

Question 11C: Predicted SAP. Early (<48 h) EN vs. PN

For *mortality* we included five RCTs (232 patients). EEN (<48 h) did not reduce the risk of death compared to PN (RR 0.61; 95% CI 0.15–2.55; $P = 0.50$; $I^2 = 41\%$). The certainty of evidence was **low**. We rated down for imprecision (Supplement 6).

For *any infections* we included five RCT (232 patients), EEN (<48 h) reduced the risk of infections compared to PN (RR 0.49; 95% CI 0.28–0.83; $P = 0.008$, $I^2 = 9\%$). The certainty of evidence was **low**. We rated down for risk of bias, inconsistency and imprecision (Supplement 6).

For *pancreatic infections* we included three RCTs (167 patients). EEN (<48 h) reduced the risk of pancreatic infections compared to PN (RR 0.40; 95% CI 0.22–0.73; $P = 0.003$; $I^2 = 0\%$). The certainty of evidence was **low**. We rated down for risk of bias and imprecision (Supplement 6). Supplement 7, Fig. 9.

Taken together, the studies in different subpopulations have demonstrated a reduction of infections but no convincing effect of EEN on mortality.

Recommendation 11. We suggest using EEN in patients with severe acute pancreatitis (Grade 2C).

Question 12: Should we delay EN in patients after GI surgery?

Out of three published meta-analyses [36–38] addressing early postoperative feeding including early oral diet, the two more recent papers [36, 37] reached different conclusions: reduced mortality and length of stay (LOS) but increased risk of vomiting analysing 15 RCTs [37] vs. no difference in mortality and LOS, but reduced complications in early group from 13 RCTs [36].

We identified three RCTs comparing early vs. delayed EN after emergency GI surgery and six RCTs in elective GI surgery. Two RCTs compared EEN vs. early PN in patients after elective GI surgery (Supplement 5, Table 12).

Question 12A: Emergency GI surgery. EEN vs delayed EN

Three RCTs (343 patients) were included. EEN did not affect mortality compared to delayed EN (RR 0.80; 95% CI 0.46–1.40; $P = 0.44$; $I^2 = 0\%$). EEN reduced the risk of infections compared to delayed EN (RR 0.61; 95% CI 0.40–0.93; $P = 0.02$; $I^2 = 0\%$). The certainty of evidence was **low**. We rated down for risk of bias and imprecision (Table 3). Supplement 7, Fig. 10.

Question 12B: Elective GI surgery. EEN vs. delayed EN

For *mortality* three RCTs (346 patients) were included. EEN did not affect mortality compared to delayed EN in patients after elective GI surgery (RR 0.83; 95% CI 0.25–2.81; $P = 0.77$; $I^2 = 17\%$). The certainty of evidence was **low**. We rated down for imprecision (Table 3).

For *any infections* six RCTs (432 patients) were included. EEN reduced the risk of infections compared to delayed EN (RR 0.43; 95% CI 0.23–0.82; $P = 0.01$; $I^2 = 46\%$). The certainty of evidence was **low**. We rated down for risk of bias and imprecision (Table 3).

Five RCTs (404 patients) reported *anastomotic leak*. EEN reduced the risk of surgical leak compared to delayed EN (RR 0.43; 95% CI 0.20–0.93; $P = 0.03$; $I^2 = 0\%$). The certainty of evidence was **low**. We rated down for imprecision (Table 3). Supplement 7, Fig. 11.

Question 12C: Elective GI surgery. EEN vs early PN

Two RCTs (440 patients) were included. EEN did not reduce the risk of pneumonia compared to early PN (RR 0.59; 95% CI 0.31–1.14; $P = 0.12$, $I^2 = 0\%$), but reduced the risk of anastomotic leak compared to early PN (RR 0.42; 95% CI 0.19–0.95; $P = 0.04$; $I^2 = 63\%$). The certainty of evidence was **low**. We rated down for risk of bias, inconsistency and imprecision (Table 3). Supplement 7, Fig. 12.

Recommendation 12. We suggest using EEN in patients after GI surgery (Grade 2C).

Question 13: Should we delay EN in patients after abdominal aortic surgery?

No RCTs but two cohort studies were identified (Supplement 5, Table 13). Cohort studies both in elective [39] and emergency repair [40] did not compare EEN with any of our comparators, but showed that EEN was successful in a minority of patients. A multimodal approach has been proposed [41], including early removal of nasogastric tubes, immediate postoperative mobilisation early oral or enteral feeding, accepting GRV up to 500 ml and use of prokinetics. Although these patients are at risk of bowel ischaemia with prevalence reported between 7 and 17% [42, 43], the risk itself should not lead to withholding EN, unless bowel ischaemia is suspected (see also Recommendation 15).

Recommendation 13. We suggest using EEN in patients after abdominal aortic surgery (Grade 2D).

Question 14: Should we delay EN in patients with abdominal trauma?

Ten RCTs and ten cohort studies addressing EEN in trauma patients (RCTs: within 6–48 h; cohort studies: within 12–96 h) were identified, but abdominal trauma specifically was addressed in six RCTs, four of them compared EEN to early PN and two EEN to delayed EN (Supplement 5, Table 14A).

Question 14A: EEN vs early PN

For *mortality* two RCTs (142 patients) were included. EEN did not affect mortality compared to early PN (RR 0.49; 95% CI 0.09–2.69; $P = 0.41$; $I^2 = 0\%$). The certainty of evidence was **very low**. We rated down for risk of bias and imprecision (Table 3).

For *any infection* four RCTs (219 patients) were included. EEN did not affect the risk of infections compared to early PN (RR 0.59; 95% CI 0.24–1.42; $P = 0.24$; $I^2 = 59\%$). The certainty of evidence was **very low**. We rated down for risk of bias, inconsistency and imprecision (Table 3). Supplement 7, Fig. 13.

Question 14B: EEN vs delayed EN

Two RCTs (101 patients) were included. EEN did not affect mortality compared to delayed EN (RR 0.74; 95% CI 0.18–3.11; $P = 0.708$). The certainty of evidence was **very low**. We rated down for risk of bias and imprecision (Table 3).

EEN did not affect the risk of infections compared to delayed EN (RR 0.83; 95% CI 0.41–1.70; $P = 0.837$). The certainty of evidence was **very low**. We rated down for risk of bias, inconsistency and imprecision (Table 3). See Supplement 7, Fig. 14.

Of note, earlier studies in this patient group almost exclusively used surgical jejunostomy for EN.

Existing evidence did not allow verifying or excluding any benefit or harm of EEN; therefore our recommendation is based on expert opinion. In addition to RCTs, nine observational studies were identified (Supplement 5, Table 14B).

An earlier meta-analysis in adult trauma patients in ICU (not specifically abdominal trauma) showed survival benefit in EEN commenced within 24 h after trauma [44].

Recommendation 14. We suggest using EEN in patients with abdominal trauma when the continuity of the GI tract is confirmed/restored (Grade 2D).

Question 15: Should we delay EN in patients with bowel ischaemia?

We identified no clinical studies, but physiological knowledge and common sense support withholding EN in patients with overt bowel ischaemia. However, patients with endoscopic evidence of mild to moderate large bowel mucosal ischaemia, without signs of transmural ischaemia or bowel distension, might profit from low dose EN. In this case we support considering EN. In a recent retrospective study, survivors were more often fed enterally before the diagnosis of acute mesenteric ischaemia, but no independent association between EN and mortality was demonstrated [45].

Recommendation 15. We suggest delaying EN in patients with overt bowel ischaemia (Grade 2D).

Question 16: Should we delay EN in critically ill adult patients with intestinal fistula?

We identified one retrospective cohort study and two case series, all showing outcome benefit of "early" EN (Supplement 5, Table 16). However, "early" was defined as EN started within 7 days or 14 days of admission. Retrospective design further diminishes the importance of these studies.

Intolerance of EN or increasing fistula output causing skin breakdown or fluid/electrolyte imbalance are evident reasons to decrease or discontinue EN [46].

Recommendation 16. We suggest delaying EN in patients with high-output intestinal fistula if reliable feeding access distal to the fistula is not achievable (Grade 2D).

Question 17: Should we delay EN in patients with an open abdomen?

Seven observational studies (one prospective cohort study, three retrospective cohort studies and four case series) were identified; two studies compared EEN (different definitions) vs delayed EN and reported higher rate of early abdominal closure, less fistula formation and lower incidence of ventilator-associated pneumonia in the "early" EN group (Supplement 5, Table 17). The largest study comparing EN to no EN in patients with open abdomen after abdominal trauma reported independent associations between EN and ultimate fascial closure and decreased mortality rate in patients without bowel injury, but no difference in a subgroup of patients with bowel injury [47].

Recommendation 17. We suggest using EEN in patients with open abdomen (Grade 2D).

Question 18: Should we delay EN in patients with intra-abdominal hypertension?

Four observational studies were identified (Supplement 5, Table 18), only one addressed early vs. delayed EN [48]. All studies reported high incidence of feeding intolerance associated with intra-abdominal hypertension, but data are not conclusive regarding causality. A recently published study demonstrated that EEN did not increase intra-abdominal pressure, but values exceeding 15 mmHg were associated with higher rates of feeding intolerance in patients with severe acute pancreatitis [48].

No prospective study addressing EN in patients with abdominal compartment syndrome [49] was identified. As abdominal compartment syndrome is an immediately life-threatening condition with jeopardized splanchnic perfusion, we suggest to withhold or stop EN and try to lower intra-abdominal pressure.

Recommendation 18a. We suggest using EEN in patients with intra-abdominal hypertension without abdominal compartment syndrome, but consider temporary reduction or discontinuation of EN when intra-abdominal pressure values further increase under EN (Grade 2D).

Recommendation 18b. We suggest delaying EN in patients with abdominal compartment syndrome (Grade 2D).

Question 19: Should we delay EN in patients with upper GI bleeding?

No studies addressing EEN were identified. One RCT in bleeding due to gastric or duodenal ulcer reported shorter hospital stay (4.2 ± 1.2 vs. 5.9 ± 1.4 days, $P < 0.001$) in the early oral feeding group [50].

EN as protection against stress ulceration and GI bleeding is suggested in one meta-analysis [51], one retrospective study in burns [52] and several reviews [53–55]. An RCT comparing ranitidine and sucralfate reported EN as an independently protective factor against GI bleeding [56]. The main rationale to prohibit eating/EN is based on fear for disturbed visibility in a further endoscopy/intervention due to rebleeding. Therefore, delaying EN for 48–72 h in patients with a high risk of rebleeding has been suggested [57]. Considering the absence of evidence to support this time frame, we suggest starting EN during the first 24–48 h after bleeding has been stopped; prolonged postponement of EN is unnecessary or even harmful because of increased risk of stress ulceration. Importantly, there is no evidence that fine-bore nasogastric tubes cause variceal bleeding [57].

Recommendation 19. We suggest delaying EN in patients with active upper GI bleeding, and starting EN when the bleeding has stopped and no signs of rebleeding are observed (Grade 2D).

Question 20: Should we delay EN in patients with acute liver failure?

We could not identify any study in acute or acute-on-chronic liver failure patients. Some benefits of EN have been shown in patients with alcoholic hepatitis, malnourished patients with cirrhosis and patients with liver transplantation [58–60], where glycogen stores may be depleted after an overnight fast and metabolic conditions resemble prolonged starvation in healthy individuals [61]. EN in fulminant acute liver failure has never been studied. These patients often present with hypoglycaemia, which should be corrected with intravenous glucose,

sometimes together with insulin. Fulminant liver failure is associated with increased serum amino acid concentrations, especially glutamine [62, 63]. It seems likely that a failing liver is unable to provide effective metabolic support required for nutrition. The pathophysiological rationale to delay EN in fulminant hepatic failure would be to "spare" the severely injured liver from the duties of metabolising and storing nutrition during a period of stress and also to avoid additional increases in ammonia. Intravenous provision of nutrients except correction of hypoglycemia and appropriate provision of vitamins and trace elements may be futile or harmful early in the clinical course [64].

Recommendation 20. We suggest starting low dose EN when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy (Grade 2D).

Remark: Arterial ammonia levels should be monitored.

Question 21: Should we delay EN in patients with large gastric aspirate volumes (GAV)?

We identified no study addressing this question. Based on existing evidence from two RCTs comparing the threshold volumes to stop already started EN [65, 66], a clear threshold volume (in ranges up to 500 ml) that increased the risk of ventilator-associated pneumonia was not identified. Measurements of GAV/GRV are not a gold standard and alternative methods (like ultrasound) can be applied to diagnose overfilling of the stomach. Gross distension of the stomach is likely to be undesirable and therefore we suggest that EN should be delayed when GAV/GRV is >500 ml/6 h [65], either for a limited time period or until administration of prokinetics. For patients with persistently large GAV/GRVs the use of postpyloric feeding should be considered rather than withholding EN, unless bowel ischaemia or obstruction is suspected (see also Recommendation 15).

Recommendation 21. We suggest delaying EN if gastric aspirate volume is above 500 ml/6 h (Grade 2D).

Question 22: Should we delay EN in patients with absent bowel sounds?

One cohort study was identified [67] (Supplement 5, Table 22). Bowel sounds are frequently absent in mechanically ventilated patients and this is associated with impaired outcome [68]. The concept that bowel sounds must be present before initiation of enteral feeding is not based on evidence and should be abandoned [69]. After laparotomy small intestinal motility is frequently preserved despite gastric and colonic paresis. The small intestine may contract silently (absence of gas), while feeding is well tolerated [69]. Gastric and colonic paresis may effectively be treated with prokinetics [70]. Initiation of EN in absence of bowel sounds might be associated with earlier return of bowel sounds, fewer episodes of vomiting, and shorter ICU and hospital stay [67].

Recommendation 22. We suggest using EEN regardless of the presence of bowel sounds unless bowel ischaemia or obstruction is suspected (Grade 2D).

Question 23: Should we delay EN in patients with diarrhoea?

There were no studies testing delay of EN in case of diarrhoea, but diarrhoea is often considered as a reason to delay EN [71]. Prevalence of diarrhoea in unselected ICU population is between 14 and 21% [72, 73]. Causes include impaired digestion/absorption, bacterial overgrowth or infection such as *Clostridium difficile*. Observational studies [74, 75] suggest that diarrhoea can be effectively managed with protocolised measures other than immediate cessation in EN. We recommend analysing the causes of diarrhoea and treat appropriately (e.g. *C. difficile* colitis). We also suggest considering treating bacterial overgrowth by selective decontamination, fibre-enriched or semi-elementary diet or digestive enzymes to reduce diarrhoea.

Recommendation 23. We suggest using EEN in patients with diarrhoea (Grade 2D).

Conclusions

We suggest using EEN, initiated at a low rate, in the majority of critically ill patients; however, the evidence is weak. Beneficial effects in terms of infection prevention have been demonstrated in unselected critically ill patients, as well as in patients with severe acute pancreatitis and after GI surgery. However, we suggest delaying EN in patients with uncontrolled shock (haemodynamic and tissue perfusion goals are not met despite of fluids and vasopressors), uncontrolled hypoxaemia and acidosis, uncontrolled GI bleeding, overt bowel ischaemia (occlusive or non-occlusive), bowel obstruction (mechanical ileus), abdominal compartment syndrome, gastric aspirate volume >500 ml/6 h or high-output fistula if reliable distal feeding access is not achievable.

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Compliance with ethical standards

Conflicts of interest
See Supplement 8.

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