



Early Enteral Versus Delayed Feeding in Critical Illness: A Narrative Review of Trials Since the Guideline Split

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Abstract

Pooled analysis of 17 randomised trials in 1,725 critically ill adults found that enteral nutrition begun within 48 hours reduced overall complications, with a risk ratio of 0.81 (95% CI 0.70 to 0.93), infectious complications at 0.68 (0.51 to 0.91) and pneumonia at 0.76 (0.60 to 0.97), and shortened hospital stay by 1.61 days. No difference was found in mortality or multiple organ failure. The benefit is therefore in morbidity rather than survival, and two qualifications follow it. Earlier meta-analyses using different methods and different definitions of early reached contradictory conclusions, and what counts as early is variously 24 or 48 hours. In patients with high illness severity, early feeding has been associated with more gastrointestinal complications and longer intensive care stay, so the direction of effect may not hold across severity. Guideline recommendations on supplemental parenteral nutrition differ between the major societies.

Keywords: Enteral nutrition; Critical illness; Timing; Meta-analysis; Guidelines

Introduction

Nutritional support in critical illness is delivered enterally where the gastrointestinal tract is usable, and the question of when to start it has been studied for three decades [1,2,3]. The proposition is that early feeding preserves gut integrity and modulates the inflammatory response, and that delay forfeits both [4,5].

Successive meta-analyses have reached contradictory conclusions about that proposition, using different methodologies and different definitions of early [1,6,7]. Recommendations on the timing of supplemental parenteral nutrition differ between the European and American societies, and the benefit of early supplemental parenteral nutrition has been questioned [1,8,9].

This review examines what the randomised evidence since that divergence supports, which outcomes move and which do not, and where the effect may reverse.

Objective

This review sets out to establish four things from the published literature. First, what pooled analysis of randomised trials shows for each outcome separately. Second, how the definition of early varies and what that does to comparability. Third, whether the effect is uniform across illness severity. And fourth, where the guidance diverges and on what point.

Literature Review

What the pooled analysis shows: A meta-analysis of 17 randomised controlled trials including 1,725 critically ill patients, 862 receiving early enteral nutrition within 48 hours of intensive care admission or operation and 863 delayed, reported significant reductions in overall complications with a risk ratio of 0.81 (95% CI 0.70 to 0.93, $p = 0.002$), in infectious complications at 0.68 (0.51 to 0.91, $p = 0.009$) and in pneumonia at 0.76 (0.60 to 0.97, $p = 0.03$) (Figure 1) [10].

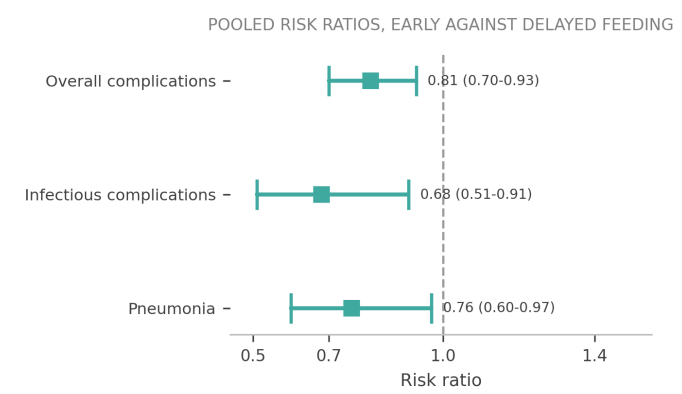


Figure 1: Pooled risk ratios for early against delayed feeding [10]

What did not move: In the same analysis no difference was found between the groups in mortality or in multiple organ failure [10]. The reduction in length of hospital stay was 1.61 days (95% CI 3.02 to 0.20 days shorter, $p = 0.03$) (Figure 3). A separate meta-analysis in gastrointestinal bleeding reported a reduction of 1.69 days (95% CI 2.15 to 1.23 shorter), with no significant difference in rebleeding at a risk ratio of 0.75 (0.34 to 1.64) or in 30-day mortality at 0.74 (0.23 to 2.39) [11].

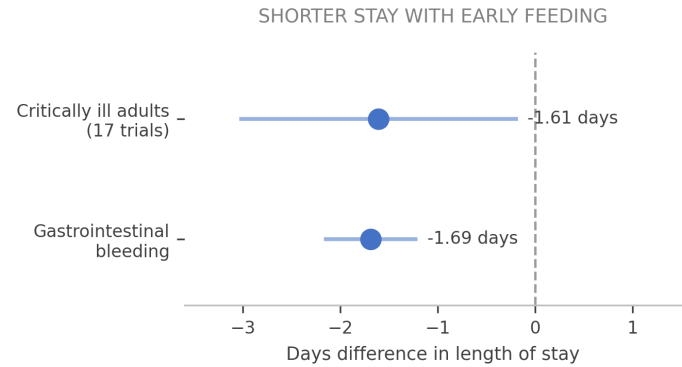


Figure 3: Difference in length of stay with early feeding [10,11]

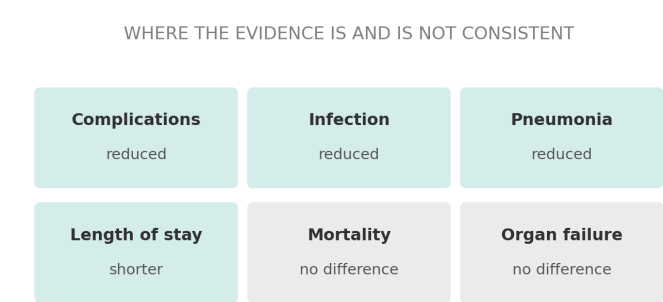


Figure 5: Outcomes that moved and outcomes that did not [10,11]

Table 1: Pooled outcomes in 1,725 critically ill adults, as published [10]

Outcome	Effect estimate	Interval
Overall complications	RR 0.81	0.70 to 0.93 [10]
Infectious complications	RR 0.68	0.51 to 0.91 [10]
Pneumonia	RR 0.76	0.60 to 0.97 [10]
Length of stay	1.61 days shorter	3.02 to 0.20 [10]
Mortality	No difference reported	— [10]

Multiple organ failure	No difference reported	— [10]
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What counts as early: Trials and reviews variously define early enteral nutrition as initiation within 24 hours or within 48 hours of admission (Figure 2) [1,10,12]. A Cochrane review compared early within 48 hours against delayed after 48 hours, with or without supplemental parenteral nutrition [1]. The gastrointestinal bleeding analysis used 24 hours [11]. Because the comparator in each case is whatever falls on the other side of the chosen line, two reviews reporting on early feeding may not be describing the same intervention [1,6].

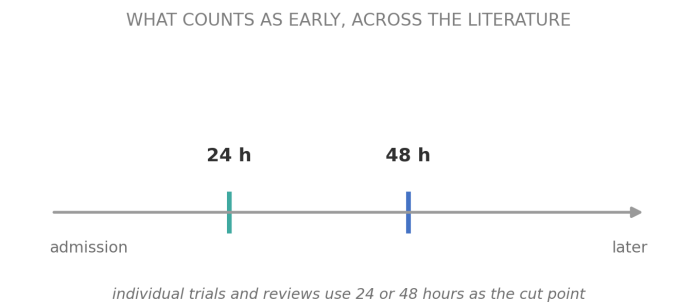


Figure 2: What counts as early, across the literature [1,10,11]

Earlier syntheses disagreed: Previously published meta-analyses in this field, using different methodologies and different definitions of early enteral nutrition, drew contradictory conclusions about the advantages in terms of mortality and hospital length of stay [1,6,7,13]. That disagreement is the immediate context for the more recent pooled estimates and is a reason to read any single figure with its definition attached [1,10].

Where the effect may reverse: Investigators have reported more gastrointestinal complications and longer intensive care stay in patients with high illness severity treated with early enteral nutrition [1,14]. Risk of treatment-related complications, including feed intolerance, gastrointestinal problems, pneumonia and other infections, is raised in the reviewed literature as a concern when considering an early start [1,15]. The pooled estimate averages across severity and cannot describe that subgroup [10,14].

The paediatric evidence: A systematic review identified four randomised trials randomising 899 children in critical care settings across three countries (Figure 4). Overall risk of bias was assessed as high risk or some concerns for all outcomes, and low-certainty evidence suggested that early enteral nutrition may reduce in-hospital mortality [12]. The certainty assessment matters more than the direction here, since the adult data found no mortality difference at higher certainty [10,12].

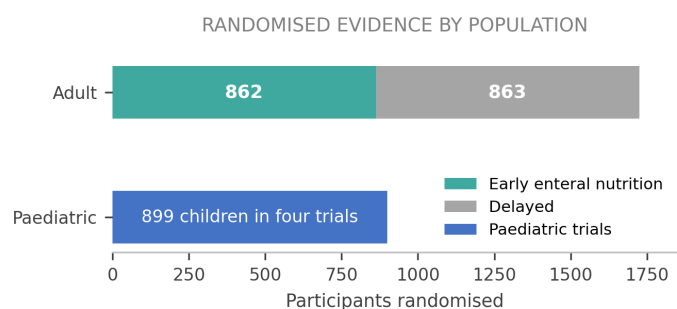


Figure 4: Randomised evidence by population [10,12]

Where the societies differ: European guidance emphasises early initiation of enteral nutrition, while the American guideline of 2022 acknowledges that early enteral or parenteral nutrition may be appropriate depending on patient condition (Figure 6) [16,17]. Recommendations on the timing of supplemental parenteral nutrition differ between the two societies, and the evidence for benefit from early supplemental parenteral nutrition has been questioned [1,8,9].

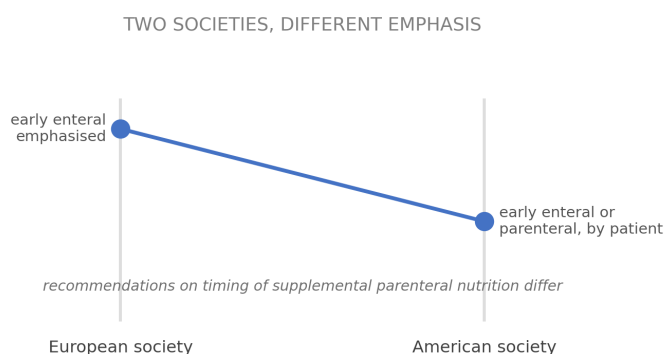


Figure 6: Emphasis of the two societies on route and timing [1,16,17]

Table 2: Why pooled estimates in this field are not directly comparable

Source of variation	Consequence for comparison
Definition of early	24 or 48 hours; comparator differs [1,11]
Supplemental parenteral nutrition	Included in some analyses, not others [1]
Illness severity	Effect may reverse at the extreme [1,14]
Population	Adult and paediatric evidence differ in certainty [10,12]

The route question sits alongside the timing one: Large randomised trials have compared enteral against parenteral routes in ventilated adults with shock [19] and in critically ill adults generally [20], and updated meta-analysis has synthesised those comparisons [23]. A separate review compared early enteral against early parenteral nutrition directly [18]. Timing and route are frequently discussed together and are separable questions with separate evidence [18,23].

How much, not only how soon: Trials of permissive underfeeding against standard enteral feeding [21] and of initial trophic against full feeding in acute lung injury [22] found that

the quantity delivered early can be reduced without detriment to the outcomes measured. Goal-directed nutrition guided by measured expenditure has been tested against standard care [34], and supplemental parenteral nutrition against usual care in a pilot randomised study [33]. Caloric and protein adequacy have separately been related to outcome in surgical patients [32]. These results complicate a simple reading of early as better, since they suggest the dose delivered in that window may matter less than its timing [21,22].

Tolerance and gastrointestinal function: Enteral feeding intolerance in mechanically ventilated patients has been characterised in a large multicentre database [26], and gastrointestinal dysfunction in critical illness reviewed with a research agenda [24,25]. Practical guidance for daily intensive care practice addresses initiation and advancement directly [27], and monitoring of nutrition in this setting has been reviewed [29]. Safety of early enteral nutrition specifically in circulatory shock has been examined [30], and propensity-matched analysis found the effect on mortality differed by noradrenaline dose [31], which is a further severity-dependent signal alongside the one described above [14,31]. Tailoring therapy to illness and recovery phase has been argued as the organising principle [28].

Table 3: What the randomised evidence does and does not establish

Question	Status in the reviewed evidence
Does early feeding reduce infection?	Yes, RR 0.68 (0.51 to 0.91) [10]
Does it reduce mortality?	No difference reported [10]
Does it shorten stay?	By about 1.6 days [10]
Does the effect hold at high severity?	Not established; may reverse [1,14]
Is the dose in that window settled?	No; trophic and permissive feeding tested [21,22]

Method

Search strategy: PubMed, the Cochrane Library and the archives of the major intensive care and clinical nutrition journals were searched for randomised trials and syntheses comparing early with delayed enteral nutrition. Search terms combined early enteral nutrition and delayed enteral nutrition with critical illness, timing, randomised and meta-analysis. Reference lists of the Cochrane review [1] and the principal pooled analysis [10] were screened by hand for primary sources.

Eligibility: Syntheses and randomised trials were included if they compared initiation of enteral nutrition at defined times in critically ill populations. Guideline documents are cited for their recommendations and identified as such. Where an outcome was reported as showing no significant difference without an accompanying effect estimate, it is reported in those terms and no estimate is supplied.

Data extraction and handling: Population, the definition of early applied, whether supplemental parenteral nutrition was permitted, and the reported estimate with its interval were extracted as published. The definition of early is stated alongside every estimate, because reviews using 24 and 48 hour thresholds are not comparing the same intervention against the same comparator, and that is central to the argument here. This review reports published findings and does not constitute guidance on the timing, route or composition of nutritional support for any patient, which is a matter for the treating team. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Concluding Remarks

The pattern across outcomes is more informative than any single estimate. Complications, infection and pneumonia all fall, with intervals excluding unity, while mortality and multiple organ failure do not move [10]. A treatment that reduces infectious complications without altering survival is doing something real, and it is not doing the thing that a mortality-framed argument would claim for it.

That distinction should govern how the intervention is described. Length of stay falls by around 1.6 days in critically ill adults and 1.7 in gastrointestinal bleeding, and both intervals exclude zero [10,11]. Those are meaningful service outcomes. They are not evidence that starting a feed earlier saves lives, and the same analyses that produced them report no mortality difference.

The definitional problem is the one most likely to mislead a reader moving between papers. Early means within 24 hours in some analyses and within 48 in others, and the delayed comparator moves with it [1,11]. A trial randomising to 20 against 30 hours and one randomising to 40 against 80 hours both report on early against delayed feeding while testing different questions, and the contradictory conclusions of earlier syntheses are partly attributable to that [1,6,7].

The severity finding deserves more weight than its single citation suggests. If early feeding produces more gastrointestinal complications and longer intensive care stay in the most severely ill, then a pooled estimate averaging across severity conceals a subgroup in whom the recommendation may be wrong [1,14]. None of the pooled analyses reviewed here reports an interaction test by severity, so the possibility remains open rather than resolved [10,14].

On the guideline divergence named in the title, the disagreement is narrower than the phrase implies and worth stating precisely. Both societies support early enteral nutrition where the gut is usable [16,17]. What differs is the position on supplemental parenteral nutrition and on when parenteral support becomes appropriate, and it is that question rather than

enteral timing on which the evidence has been questioned [1,8,9].

Three limitations belong with these conclusions. The pooled estimates combine trials with different definitions of early, different comparators and different permission for supplemental parenteral nutrition, so heterogeneity is structural rather than incidental [1,10]. The paediatric evidence rests on four trials with high risk of bias or some concerns across all outcomes, and low certainty by formal assessment [12]. And where a source reported no significant difference without publishing an effect estimate, this review says so rather than supplying one, which means the absence of effect is less precisely characterised than the presence of it [10].

A practical reading follows from separating the questions the literature runs together. Whether to feed enterally when the gut works is settled and both societies agree [16,17]. Whether to begin within 24 or 48 hours is what the trials actually randomised, and the answer is that earlier reduces complications without changing survival [10]. Whether to add parenteral nutrition alongside it is the point of real disagreement, and the trials addressing it are separate from those pooled here [8,9,33].

The dose question complicates the timing one in a way worth stating. Trials of permissive underfeeding and of trophic feeding found no detriment from delivering substantially less in the early period [21,22]. If the quantity delivered early can be reduced without harm, then what early feeding achieves may depend less on nutrient delivery than on the presence of feed in the gut, which is a different mechanism and would predict a different dose-response [4,5,22].

Finally, the severity signal appears twice in this literature from different directions. Higher illness severity has been associated with more gastrointestinal complications under early feeding [14], and propensity-matched analysis found the mortality effect differed by vasopressor dose [31]. Two independent signals pointing at the same modifier is a stronger reason to doubt uniformity than either alone, and an interaction test by severity would be more informative than a further pooled estimate [10,14,31].

There is a design point that would resolve more than another pooled estimate. Every synthesis reviewed here reports a single average effect across trials that randomised at different thresholds, permitted different amounts of supplemental parenteral nutrition and enrolled patients of different severity [1,10]. A trial randomising a defined severity band to feeding at a stated hour, with the dose in that window specified rather than left to protocol, would answer a question none of the existing evidence quite asks [10,21,22].

The gap between what is measured and what is recommended is worth naming plainly. Guidance addresses when to start and by which route [16,17]. The trials measure complications, infection, pneumonia, stay and mortality [10,11]. Nothing

reviewed here reports functional recovery or quality of life after discharge, and the reviewers of the route comparison note that studies of longer-term outcomes such as ninety-day mortality and functional recovery are needed [18]. For a population in whom survival is increasingly expected, that omission is the more consequential one [18,28].

A closing observation about how this literature reads. The direction of effect is consistent and the mechanism plausible, which makes early feeding easy to advocate in general terms [4,5,10]. The disagreements that remain are specific: the hour chosen, the dose delivered in that window, the place of supplemental parenteral nutrition, and whether the sickest patients behave like the rest [1,14,21,31]. Those are the questions a bedside decision actually turns on, and they are the ones the pooled estimates are least able to settle [10,14].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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