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Early Versus Delayed Feeding in Patients With Acute Pancreatitis

A Systematic Review

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Background: Acute pancreatitis is among the most common and costly reasons for hospitalization in the United States. Bowel rest, pain control, and intravenous fluids are the cornerstones of treatment, but early feeding might also be beneficial.

Purpose: To compare length of hospital stay, mortality, and readmission in adults hospitalized with pancreatitis who received early versus delayed feeding.

Data Sources: MEDLINE via Ovid, EMBASE, the Cochrane Library, CINAHL, and Web of Science through January 2017.

Study Selection: Two authors independently reviewed and selected studies if they were randomized clinical trials, included adults hospitalized with acute pancreatitis, and compared early versus delayed feeding (≤48 vs. >48 hours after hospitalization).

Data Extraction: Two investigators independently extracted study data and rated risk of bias using the Cochrane Collaboration tool.

Data Synthesis: Eleven randomized trials (8 peer-reviewed publications, 3 abstract-only presentations) that included 948 patients were eligible. Seven trials (3 with low risk of bias) enrolled patients with mild to moderate pancreatitis. Four trials (1 with low risk of bias) included patients with predicted severe pancreatitis. Routes used for early feeding included oral (4 studies), nasogastric (2 studies), nasojejunal (4 studies), and oral or nasoenteric (1 study). Among patients with mild to moderate pancreatitis, early feeding was associated with reduced length of stay in 4 of 7 studies (including 2 of 3 with low risk of bias). Other outcomes were heterogeneous and variably reported, but no study showed an increase in adverse events with early feeding. Among patients with severe pancreatitis, limited evidence revealed no statistically significant difference in outcomes between early and delayed feeding.

Limitation: Heterogeneity of feeding protocols and outcomes, scant data, and unclear or high risk of bias in several studies.

Conclusion: Limited data suggest that early feeding in patients with acute pancreatitis does not seem to increase adverse events and, for patients with mild to moderate pancreatitis, may reduce length of hospital stay.

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Acute pancreatitis is a common cause of hospitalization worldwide (1), and recent data suggest that incidence is increasing (2). Treatment of pancreatitis usually consists of early recognition, aggressive intravenous hydration, pain control, and supportive monitoring. Oral intake during an episode of acute pancreatitis is believed to stimulate pancreatic exocrine activity and potentially prolong recovery. For this reason, bowel rest, including nothing-by-mouth status (NPO), has been the standard of care since at least 1950 (3). Keeping patients NPO, however, necessitates prolonged hospitalization or other forms of nutrition, both of which may increase risk for adverse events.

Data suggest that enteral nutrition helps stimulate the gut and maintain its protective barrier, thus reducing bacterial overgrowth and preventing bacterial translocation and sepsis (4–6). Several reviews of patients with pancreatitis suggest that those who receive enteral feeding have fewer infections, shorter hospital stays, and lower mortality than those who receive total parenteral nutrition (7–11). In addition, enteral feeding in patients with acute pancreatitis may reduce length of hospital stay when given early (12). Despite these data, whether to feed patients with pancreatitis during an active phase of inflammation or to delay feeding until the acute phase has subsided remains controversial. Recent trials comparing early versus delayed feeding have yielded mixed results, and available guidelines are vague and contradictory (13, 14). Physician practice varies, with up to 94% of patients being placed NPO at admission (15, 16). The aim of this systematic review of randomized clinical trials was to evaluate whether early feeding affects length of hospital stay, symptoms, and clinical outcomes compared with delayed feeding in patients hospitalized with acute pancreatitis.

METHODS

We developed a protocol (PROSPERO: CRD42015 016193) and followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) recommendations (17).

Data Sources and Searches

Between 25 March 2015 and 6 January 2017, a medical librarian (M.L.C.) performed serial literature searches for randomized controlled trials in the following databases: MEDLINE via Ovid (start date, 1950), EMBASE (start date, 1946), the Cochrane Library (start date, 1948), CINAHL (start date, 1960), and Web of Science (start date, 1996). Searches designed for each da-

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tabase included controlled vocabulary terms (for example, Medical Subject Headings) when available, combined with keywords to represent concepts, including "pancreatitis," "fast," "NPO," "delayed feeding," and "enteral nutrition" (see the **Appendix**, available at Annals.org, for all search details). No restrictions were placed on publication date, language, or completion status. We also searched ClinicalTrials.gov (23 December 2016), hand-searched bibliographies of trials and reviews, and contacted content experts.

Study Selection

Randomized controlled trials were eligible for inclusion if they compared early versus delayed enteral nutrition in adults hospitalized with a diagnosis of acute pancreatitis. In keeping with prior reviews and guidelines (18, 19), we defined early feeding as feeding initiated at or within 48 hours of hospitalization and delayed feeding as feeding initiated more than 48 hours after hospitalization. Studies were excluded if they compared enteral versus parenteral nutrition, compared one form of enteral nutrition with another without varying timing of feeding, or compared one type of feeding formula with another. We considered studies published in any language and in full-text, abstract, or poster form eligible for inclusion. Two authors (V.M.V. and D.S.) independently determined study eligibility; when necessary, differences in opinion were resolved by a third author (V.C.). Interrater agreement for study eligibility and data abstraction was assessed using the Cohen κ coefficient. Study authors were contacted to ascertain study eligibility or clarify data.

Data Extraction and Quality Assessment

Data were extracted from included studies independently and in duplicate by 2 authors (V.M.V. and D.S.) using a template adapted from the Cochrane Collaboration (20). Information on the number and type of patients, definitions of early and delayed feeding, type of feeding, and outcomes (length of hospital stay, mortality, readmission, and symptoms) was extracted.

Two authors (V.M.V. and D.S.) independently assessed risk of bias in included trials for the outcome of length of stay by using the Cochrane Collaboration tool (20). Studies that met low-risk criteria in each of the 6 domains were designated as having low risk of bias. Studies were classified as having unclear risk of bias if methodological data were missing. Because blinding of patients and clinicians was not feasible and blinding of data collectors and outcome adjudicators was unlikely to affect length of stay, we considered all studies to be at low risk of bias for the blinding domain.

Data Synthesis and Analysis

We qualitatively synthesized results of studies that included patients with mild to moderate pancreatitis separately from those that included patients with severe pancreatitis. Our main outcomes of interest were length of hospital stay, mortality, and readmission. Secondary outcomes included feeding intolerance, nausea, vomiting, recurrent abdominal pain, and necrotizing pancreatitis. We reported length of stay using the summary statistic (mean or median) provided by individual studies. One study (21) had 2 early-feeding groups, so the means and SDs of the groups were combined (20). For this study, the number of patients in each group was not provided, so an equal split was assumed. For the remaining outcomes, risk differences were calculated as the difference in the proportion of patients in each group who developed an adverse event. Because of clinical heterogeneity of patient populations, feeding protocols, and reported outcomes, meta-analysis was not performed.

Role of the Funding Source

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RESULTS

Search Results and Study Details

A total of 1212 citations were retrieved by our search. An additional 107 studies were obtained through review of references and ClinicalTrials.gov. Of these 1319 citations, 8 peer-reviewed randomized clinical trials (22–29) and 3 conference abstracts (21, 30, 31) that included 948 patients met eligibility criteria (**Figure 1**). Interrater agreement for study eligibility was 0.86. Eight studies were conducted in Europe, and the other 3 were done in New Zealand, the United States, and China.

Four of the 11 trials were determined to have low risk of bias using the Cochrane tool (**Table 1** and **Appendix Table**, available at Annals.org) (24, 26, 28, 29). The Cohen κ coefficient for adjudication of study bias was 0.87.

Patient Characteristics

Acute pancreatitis was uniformly defined across studies as 2 or more of the following: typical abdominal pain, a serum lipase or amylase level at least 3 times the upper limit of normal, and characteristic findings on imaging. Patients with chronic (24, 26, 28, 29), recurrent (25), postendoscopic retrograde cholangiopancreatography (24, 28), or tumor-related (24, 28) pancreatitis were variably excluded from studies. Most studies (24, 26–30) followed the usual standard of care (for example, intravenous fluids or pain control) for patients with pancreatitis; however, 3 studies (22, 23, 25) included intravenous antibiotics, and 1 (23) included intermittent parenteral nutrition. Total parenteral nutrition was permitted at the treating physician's discretion in 3 of the 11 studies (23, 24, 28).

Severity of pancreatitis was variably defined and included such assessments as the Atlanta criteria, APACHE (Acute Physiology and Chronic Health Evaluation) score, Ranson criteria, computed tomography classification, or organ failure; however, APACHE II scores were used most frequently (**Table 1**) (22–26). Four studies included patients with predicted moder-

ate to severe (25) or severe (22–24) pancreatitis. The incidence of severe pancreatitis in these studies varied from 27% to 100%, and mean APACHE II scores varied from 9.8 to 11 (22, 24, 25). The 7 remaining studies included patients with mild (21, 26, 27, 29, 31) or mild to moderate (28, 30) pancreatitis.

Route of Feeding

For studies of patients with mild to moderate pancreatitis, the route of feeding in the early group varied: 4 administered oral feeding (26, 27, 29, 31), and 2 administered nasogastric feeding (28, 30). One study (21) randomly assigned patients in the early group to either early oral or early nasoenteric feeding. All control groups in studies of patients with mild to moderate pancreatitis were fed orally. In contrast, all 4 studies of patients with predicted severe pancreatitis provided the early group with nasojejunal feeding, whereas the delayed group received either oral (22, 24, 25) or nasojejunal feeding (23).

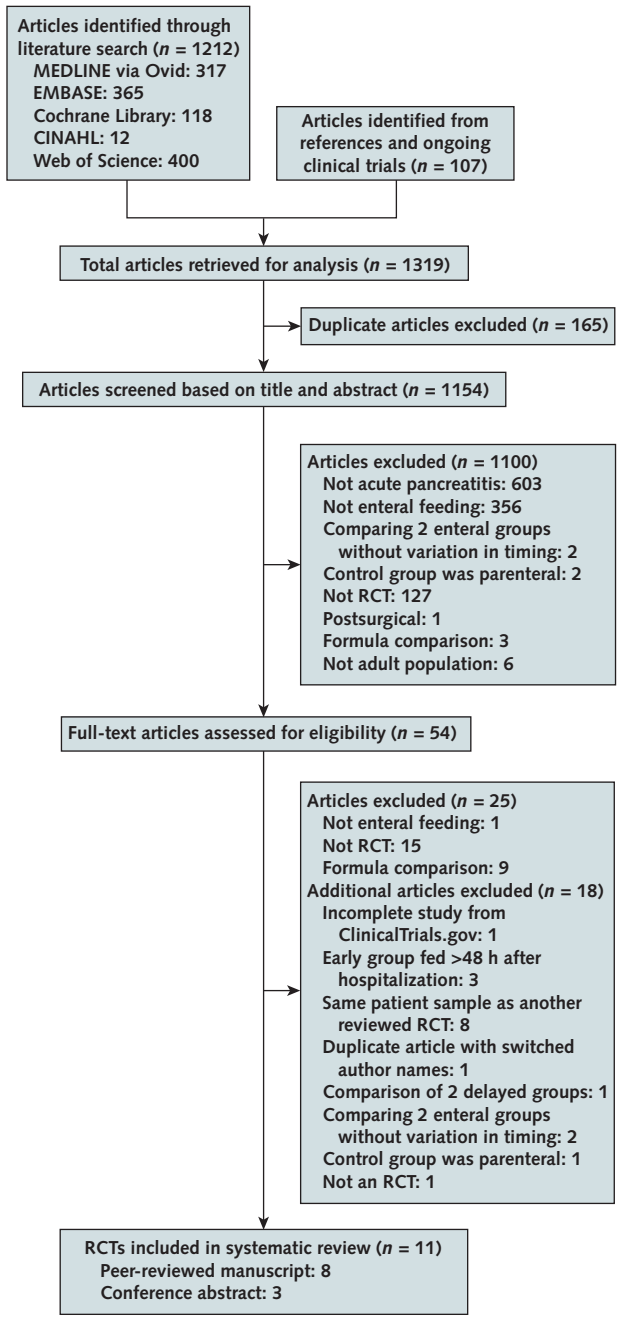
Oral diets varied from white bread with jam and tea (27) to regular diet. One study randomly assigned patients in each group to receive a full-calorie diet or stepwise increases in nutrition (29). Generally, patients who did not tolerate an oral diet were kept NPO or were provided nasoenteric or parenteral nutrition at the treating physician's discretion. In general, enteral feeding had no minimum duration; however, in the largest trial (25), patients who received early enteral nutrition were required to receive it for 7 days per protocol.

Timing of Feeding

Criteria for initiation of feeding varied for the early and delayed groups. Five of the 7 studies that included patients with mild pancreatitis defined early feeding as occurring within 24 hours of admission (21, 26, 28, 30, 31), using such terms as "immediately" (26) or "at the next meal time" (31), and 2 studies initiated feeding using clinical criteria, such as once the patient stopped opiate therapy (27) or had bowel sounds (29). For the delayed groups, 3 studies used improvement in pancreatic enzyme levels as the criterion (21, 27, 29), and the remaining 4 required a "period of fasting" (26, 28, 30, 31) that was not otherwise defined. Mean time to initiation of feeding for the delayed groups ranged from 2.7 to 5.5 days (26, 30).

All 4 studies of patients with severe pancreatitis used a time cutoff for initiation of early nasojejunal feeding (24, 48, or 72 hours) (22–25). Mean time to enteral feeding in the early groups ranged from 0.3 to 1.3 days, and mean time to first oral feeding ranged from 3.0 to 5.6 days (22, 23, 25). For the delayed groups, 2 studies offered a diet on hospital day 3 (24, 25), 1 placed a nasojejunal tube after 48 hours to start feeding (23), and 1 fed according to "conventional therapy" (22). Time to first feeding for the delayed groups thus ranged from 2.4 to 6.0 days (22, 24), and time to first oral feeding ranged from 2.4 to 6.4 days (23, 24). Of note, the delayed group in the second-largest study (24) fasted for only 2.4 days (64 hours), whereas that of the largest study (25) fasted for only 3 days.

Figure 1. Flow diagram of study selection.



RCT = randomized clinical trial.

Main Outcomes

Length of hospital stay was reported in all studies as either mean and SD (21, 23, 25, 30, 31) or median with range (22), interquartile range (24, 27, 28), or a box plot figure (26, 29) (Table 2 and Figure 2). In 4 of 7 studies of patients with mild pancreatitis, including 2 studies with low risk of bias (26, 29) and 2 with unclear risk (30, 31), early feeding was associated with reduced length of stay compared with delayed feeding. One

Table 1. Characteristics of Included Randomized Clinical Trials

Study, Year (Reference)	Country	Publication Status	Patients, *n*		Severity of Pancreatitis* (Criteria)	Mean Time to Any Feeding (SD), *d*†	
			Early	Delayed		Early	Delayed
Mild/moderate pancreatitis							
Badalov et al, 2007 (21)	United States	Abstract	22§	11	Mild (<3 Ranson criteria, APACHE score >6, and no necrosis or organ dysfunction)	NR	NR
Eckerwall et al, 2007 (26)	Sweden	Full text	29	30	Mild (APACHE II score and CRP level)	0.3 (0.8)‖	2.7 (0.8)
Teich et al, 2010 (27)	Germany	Full text	69	74	Mild (no organ support or TPN)	2.0 (1.5)	3.0 (1.5)
Petrov et al, 2013 (28)	New Zealand	Full text	17	18	Mild to moderate (no organ failure or pancreatic infection)	0.8 (0.2)	4.2 (2.0)
Karabulut et al, 2014 (31)	Turkey	Abstract	49	49	Mild (Atlanta criteria)	NR	NR
Larĭno-Noia et al, 2014 (29)	Spain	Full text	37	35	Mild (Atlanta criteria)	2.4 (0.8)	4.3 (2.1)
Kurti et al, 2015 (30)	Albania	Abstract	21	20	Mild to moderate (NR)	<1.0 (NR)	5.5 (NR)
Severe pancreatitis							
Powell et al, 2000 (22)	United Kingdom	Full text	13	14	Severe (Glasgow score ≥3; APACHE II score ≥7)	0.3 (0.4)	6 (4–10)**
Wu et al, 2008 (23)	China	Full text	23	20	Severe (CT classification and APACHE II score)	1.3 (NR)	4.5 (1.3)
Bakker et al, 2014 (24)	The Netherlands	Full text	101	104	Severe (APACHE II and modified Glasgow scores and CRP level)	0.4 (0.6)‡‡	2.4 (0.3)
Stimac et al, 2016 (25)	Croatia	Full text	107	107	Moderate to severe (APACHE II score ≥6)	0.2 (0.1)	3 (NR)

APACHE = Acute Physiology and Chronic Health Evaluation; CRP = C-reactive protein; CT = computed tomography; LOS = length of stay; NR = not reported; SIRS = systemic inflammatory response syndrome; TPN = total parenteral nutrition; ULN = upper limit of normal.
* Classification system that study authors used to define severe pancreatitis. An APACHE II score ≥8, a CRP level >1428.6 nmol/L, a CT classification of D or E, or a modified Glasgow score ≥3 indicated severe pancreatitis. The Atlanta criteria classified pancreatitis as severe if organ failure or local complications developed.
† Includes time to oral or nasoenteric (nasogastric/nasojejunal) feeding.
‡ Assessed using the Cochrane Collaboration tool. For breakdown of risk, see the **Appendix Table** (available at Annals.org).
§ The abstract did not provide this value for each study group. An equal split among the 3 groups (early nasoenteric, early oral, and delayed oral) was assumed.
‖ Median value was 0 d (interquartile range, 0 to 1 d).
¶ Feasibility was evaluated by abdominal pain (on day 3 and at discharge based on visual analogue scale) and frequency of gastrointestinal symptoms (combined nausea, vomiting, gripes, and diarrhea).
** Median (interquartile range).
†† This value was NR. Reported instead is "time to recovery of gut function" (borborygmus, defecation, and no abdominal pain or distention), which was the time at which full feeding was initiated.
‡‡ Median was 0.33 d (interquartile range, 0.08 to 0.83 d).

study of patients with severe pancreatitis (high risk of bias) did not assess the association between early feeding and length of stay (22). Of the remaining 3 studies of patients with severe pancreatitis, only 1 (unclear risk of bias) found early feeding to be associated with reduced length of stay (23). However, this study was small and did not report mortality.

Among the 5 studies that included patients with mild pancreatitis and reported mortality (3 with low risk of bias, 1 with unclear risk, and 1 with high risk), no deaths were reported (26–29, 31). One study (low risk of bias) of patients with severe pancreatitis reported incidence of death of 8.8%, and another study (unclear risk of bias) reported incidence of 12.6% (24, 25). Neither reported a statistically significant association between early feeding and mortality (**Appendix Figure 1**, available at Annals.org). Readmission rates were reported in only 2 trials (26, 28); both studies included patients with mild to moderate pancreatitis, and both were assessed as having low risk of bias. Neither trial reported a significant association between early feeding and readmission (**Appendix Figure 2**, available at Annals.org).

Secondary Outcomes

In 4 studies of patients with mild to moderate pancreatitis (26, 28–30), feeding was stopped if patients developed severe worsening pain, vomiting, or ileus. In these cases, "feeding intolerance" was recorded and feeding was reattempted after the symptoms improved or on the following day. Two of these studies (1 with low risk of bias and 1 with unclear risk [28, 30]) found a statistically significant association between early feeding and less feeding intolerance (**Appendix Figure 3**, available at Annals.org). In 1 study (unclear risk of bias) of patients with severe pancreatitis, feeding intolerance was defined as inability to tolerate a low-fat diet on the fifth day (25). No difference in this outcome between the early and delayed groups was noted. Another study (low risk of bias) of patients with severe pancreatitis reported that 31% of patients in the delayed group required nasoenteric feeding due to intolerance of an

Table 1–Continued

Mean Time to Oral Feeding (SD), *d*		Criteria for Initiation of Feeding		Route of Feeding		Risk of Bias‡	Primary Outcome
Early	Delayed	Early	Delayed	Early	Delayed		
NR	NR	Within 12 h of hospitalization	Until pain resolved and amylase level was <3 times the ULN	Split between oral and nasoenteric	Oral	Unclear	NR
0.3 (0.8)	2.7 (0.8)	Immediately	After a period of fasting	Oral	Oral	Low	LOS; lipase level; SIRS; feasibility¶
2.0 (1.5)	3.0 (1.5)	Off opiate therapy	Lipase level <2 times ULN	Oral	Oral	High	LOS; pain after first food intake
4.7 (2.4)	4.2 (2.0)	Nasogastric ≤24 h after admission	Nothing by mouth until physician decision	Nasogastric	Oral	Low	LOS
NR	NR	Next mealtime	"Routine feeding"	Oral	Oral	Unclear	NR
2.4 (0.8)	4.3 (2.1)	Bowel sounds present	No pain or fever; decreasing lipase level and leukocyte count	Oral	Oral	Low	LOS
3.1 (NR)	5.5 (NR)	Nasogastric ≤24 h after admission	After a period of fasting	Nasogastric	Oral	Unclear	LOS
5 (4–9)**	6 (4–10)**	Within 72 h of disease onset	Conventional therapy	Nasojejunal	Oral	High	Markers of the inflammatory response
5.6 (1.1)††	6.4 (1.1)	Nasojejunal ≤48 h after admission	Nasojejunal after 48 h	Nasojejunal	Nasojejunal	Unclear	LOS; APACHE II score; CRP level; cost
NR	2.4 (0.3)	Nasojejunal ≤24 h after admission	Oral offered at 72 h; nasojejunal if oral not tolerated	Nasojejunal	Oral	Low	Composite major infection or death
3 (NR)	3 (NR)	Nasojejunal ≤24 h after admission	Clear liquid diet on day 3	Nasojejunal	Oral	Unclear	SIRS

oral diet at 72 hours (24). Feeding intolerance for the early group was not reported.

A range of gastrointestinal symptoms, including nausea, bloating, diarrhea, abdominal pain, and vomiting, was reported across studies, each determined clinically (26), via a visual analogue scale (27, 28), or using a study-specific scale (22, 29). Two studies (low risk of bias) of patients with mild pancreatitis reported the proportion with nausea and the proportion with vomiting, with rates ranging from 4.2% to 42.4% (26, 29). There was no association between early feeding and proportions of patients with either nausea or vomiting. One study (low risk of bias) (28) reported the combined proportion of patients with nausea or vomiting and found early feeding to be associated with reduced rates of this outcome (**Appendix Figure 4**, available at Annals.org). Only 1 study of patients with severe pancreatitis reported the proportion with nausea and the proportion with vomiting (24); this study (low risk of bias) found no association between early feeding and either symptom. In the single study (high risk of bias) of patients with severe pancreatitis that reported daily nausea scores, enteral nutrition did not significantly affect nausea (22).

All 7 studies of patients with mild to moderate pancreatitis reported measures of abdominal pain; 3 (1 with low risk of bias and 2 with unclear risk) found a reduction in abdominal pain with early feeding (28, 30, 31). Rates of recurrent abdominal pain were reported in 3 studies, all of which were deemed to have low risk of bias (26, 28, 29); rates ranged from 29.2% to 54.3% (28, 29). None found a difference in rates of recurrent abdominal pain between early and delayed feeding (**Appendix Figure 5**, available at Annals.org). Three studies of patients with mild to moderate pancreatitis reported pain measured by scales; 2 (1 with low risk of bias [28] and 1 with unclear risk [31]) found a reduction in "mean pain index" with early versus delayed feeding, whereas the third study (high risk of bias) reported no difference in pain (27). Two studies of patients with mild to moderate pancreatitis compared narcotic use between early and delayed groups: 1 study (unclear risk of bias) found no difference in such use (21), and the other (low risk of bias) reported a statistically significant reduction 24 and 48 hours after randomization in those receiving early feeding (28). An additional study (unclear risk of bias) also reported a shorter duration of pain (3.1 vs. 4.5 days; $P < 0.05$) with early versus delayed feeding (30).

Only 2 studies that included patients with severe pancreatitis reported measures of abdominal pain. One study (unclear risk of bias) reported rates of recurrent abdominal pain (25), and the other (low risk of bias) reported daily pain scores (24); neither found a difference in pain between early and delayed feeding.

Necrotizing pancreatitis, diagnosed by computed tomography, was reported in 3 studies (2 with low risk of bias and 1 with unclear risk) (24–26). The 2 studies that included patients with severe pancreatitis (24, 25) had high rates of necrotizing pancreatitis (32.7% and 62.9%), whereas 1 study of patients with mild pancreatitis (26) had no such events. No studies showed an association between early feeding and necrotizing pancreatitis (**Appendix Figure 6**, available at Annals.org). One study (high risk of bias) of patients with severe pancreatitis reported Balthazar computed tomography

Table 2. Summary of Reported Outcomes in Randomized Controlled Trials Assessing Early Versus Delayed Feeding in Patients With Acute Pancreatitis

Study, Year (Reference)	Mean LOS (SD), *d*		Median LOS (IQR), *d*		Death, *n (%)*		Readmission, *n (%)*	
	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed
Mild/moderate pancreatitis								
Badalov et al, 2007 (21)	Oral: 4.1 (1.7) Nasoenteric: 3.8 (2.5) Both: 4.0 (2.1)†	4.2 (1.1)	NR	NR	NR	NR	NR	NR
Eckerwall et al, 2007 (26)	NR	NR	4 (3–6)	6 (4–9)	0 (0)	0 (0)	2 (6.9)	3 (10.0)
Teich et al, 2010 (27)	NR	NR	7.0 (5.0–10.5)	8.00 (5.75–12.00)	0 (0)	0 (0)	NR	NR
Petrov et al, 2013 (28)	NR	NR	9 (5–12)	8.5 (6.0–13.0)	0 (0)	0 (0)	1 (5.9)	2 (11.1)
Karabulut et al, 2014 (31)	3.9 (0.7)	4.9 (0.8)	NR	NR	0 (0)	0 (0)	NR	NR
Larĩno-Noia et al, 2014 (29)	NR	NR	5 (3–15)‡	7 (4–18)‡	0 (0)	0 (0)	Did not follow patients past discharge	
Kurti et al, 2015 (30)	8.4 (1.8)	10.2 (2.0)	NR	NR	NR	NR	NR	NR
Severe pancreatitis								
Powell et al, 2000 (22)	NR	NR	10 (5–30)‡	10 (5–94)‡	NR	NR	NR	NR
Wu et al, 2008 (23)	23.5 (5.3)	27.7 (7.4)	NR	NR	NR	NR	NR	NR
Bakker et al, 2014 (24)	NR	NR	15 (10–22)	14 (9–25)	11 (10.9)	7 (6.7)	NR	NR
Stimac et al, 2016 (25)	16.7 (8.7)	15.5 (8.1)	NR	NR	10 (9.3)	17 (15.9)	NR	NR

CT = computed tomography; IQR = interquartile range; LOS = length of stay; NR = not reported.
* For studies reporting nausea and vomiting separately, only data for patients with nausea are presented (see **Appendix Figure 4** [available at Annals.org] for data on both).
† The early group was randomly assigned to early oral and early nasoenteric feeding. The combined data were calculated from the summary estimates.
‡ Values in parentheses are ranges.

scores (which reflect the extent of pancreatic necrosis) on days 7 and 14 and found no difference between early and delayed feeding (23).

DISCUSSION

When to feed patients hospitalized with acute pancreatitis has been controversial for decades. Although studies of patients with sepsis suggest benefit from early feeding (32), compelling data to make the same argument in those with pancreatitis have been lacking. In this systematic review, we evaluated 11 randomized trials of early versus delayed feeding that included 948 patients with acute pancreatitis. Although heterogeneous protocols and outcomes, no study showed a statistically significant increase in adverse events or worsening of symptoms with early feeding, regardless of disease severity. For patients with mild to moderate pancreatitis, early feeding was associated with reduced length of hospital stay in 4 of 7 studies, including 2 with low risk of bias. Gastrointestinal symptoms, such as feeding intolerance, nausea, vomiting, and abdominal pain, were less frequent among patients randomly assigned to early feeding in 3 studies, including 1 with low risk of bias that showed a reduction in all 4 symptoms. Only 1 study of patients with severe pancreatitis had low risk of bias and reported no difference in length of stay, mortality, symptoms, or necrotizing pancreatitis between patients randomly assigned to early versus delayed feeding. Collectively, these results suggest that early feeding may be a safe alternative to fasting in some patients with pancreatitis.

That early feeding was not associated with increased complications and may be associated with shorter hospital stay reflects scientific evidence about the role of nutrition in acute pancreatitis. It is generally accepted that enteral feeding, when feasible, is superior to total parenteral nutrition (7–11, 18). New evidence, however, suggests that enteral feeding may have benefits that could decrease length of stay, such as reduced intestinal permeability, improved gut motility, and reduced infection of pancreatic necrosis (33–36). Even small amounts of enteral nutrition may help preserve intestinal epithelium and epithelial tight cell junctions, stimulate secretion of brush border enzymes, enhance immune function, or prevent bacterial translocation (37–39). In critically ill patients, early feeding has recently been recognized as an important therapeutic intervention, including for those with severe sepsis and

Table 2–Continued

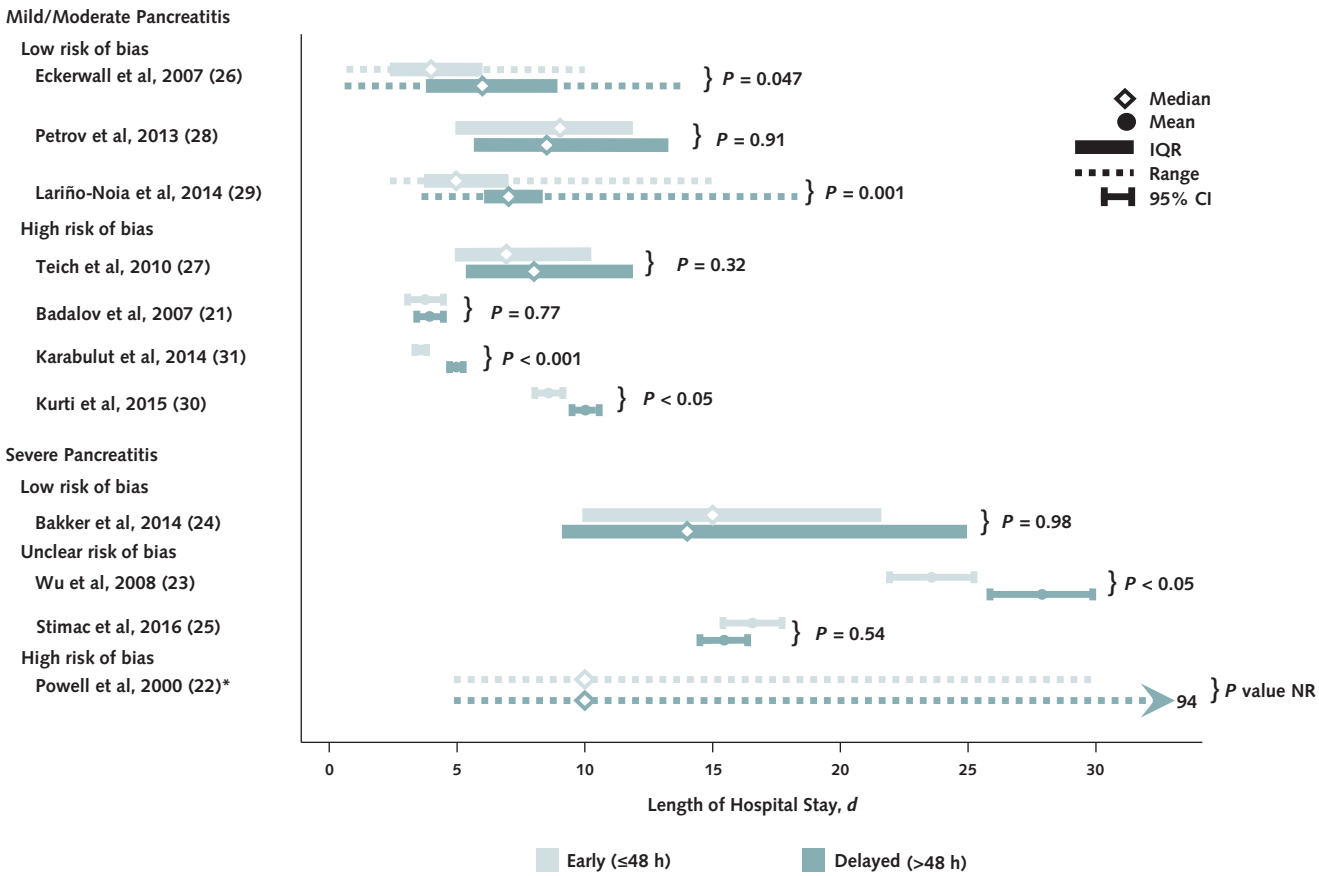
Feeding Intolerance, *n (%)*		Nausea and/or Vomiting, *n (%)**		Recurrent Abdominal Pain, *n (%)*		Necrotizing Pancreatitis, *n (%)*	
Early	**Delayed**	**Early**	**Delayed**	**Early**	**Delayed**	**Early**	**Delayed**
NR	NR	NR	NR	No difference in narcotic use		NR	NR
1 (3.4)	4 (13.3)	9 (31.0)	16 (53.3)	9 (31.0)	9 (30.0)	0 (0)	0 (0)
NR	NR	NR	NR	No difference in change in pain scores before and after first meal		NR	NR
1 (5.9)	9 (50.0)	0 (0)	6 (33.3)	7 (41.2)	12 (66.7)	NR	NR
				Fewer opiates and less pain			
NR	NR	NR	NR	"Mean pain index" lower in the early group		NR	NR
4 (10.8)	4 (11.4)	4 (10.8)	3 (8.6)	12 (32.4)	9 (25.7)	NR	NR
1 (4.8)	6 (30.0)	NR	NR	Shorter duration of pain in the early group		NR	NR
NR	NR	Enteral nutrition did not affect daily nausea scores		NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	Balthazar CT scores on days 7 and 14 did not differ	
NR	32 (30.8)	32 (31.7)	37 (35.6)	No difference in daily pain scores		64 (63.4)	65 (62.5)
65 (60.7)	57 (53.3)	NR	NR	4 (3.7)	0 (0)	37 (34.6)	33 (30.8)

septic shock, for whom oral or enteral feeding is now recommended within 48 hours after diagnosis (19, 40). Recent reviews of acute pancreatitis have also suggested that early enteral feeding may be beneficial. In a meta-analysis of observational data from patients with acute pancreatitis, feeding within 72 hours was associated with not only shorter hospital stay but also lower rates of mechanical ventilation, pancreatic infection, and mortality (41). A recent systematic review and meta-analysis of early feeding in patients with mild pancreatitis, which included 3 studies we reviewed and 2 we excluded (42, 43), showed a significant association between early feeding and shorter hospital stay (12). In combination, these data suggest that early feeding may be beneficial, particularly in patients with mild pancreatitis.

Despite these encouraging results, questions persist about feeding in patients with pancreatitis. First, the implications of these findings for patients with severe pancreatitis remain uncertain. Although none of the 4 studies of such patients found an increase in adverse events with early feeding, only 1 showed benefit (23). This study found reduced length of stay with early feeding; however, it did not report mortality and had methodological flaws that limit the value of its conclusions. Given these limitations, the utility of early feeding in this population remains to be seen. Second, our study was not designed to assess the initial route of feeding, which varied considerably across trials. The timing of early feeding also varied; therefore, an exact definition of early feeding does not exist, limiting recommendations on when it should begin. Finally, the preferred course for a patient who does not tolerate an initial oral diet is unknown. In the included studies, these patients were kept NPO, transitioned to enteral feeding, or placed on total parenteral nutrition. Further studies to answer these questions are necessary.

This study has several strengths, including an explicit, published protocol and a comprehensive literature search that included gray literature and spanned peer-reviewed articles, abstracts, and ongoing trials. The searches allowed inclusion of data that have not been included elsewhere, including 3 abstracts (21, 30, 31) and 1 foreign-language publication (23). Inclusion of this type of gray literature may help offset publication bias. Unlike past reviews (7–11), we excluded trials with total parenteral nutrition as a comparator given that it is no longer considered the standard of care for treatment of acute pancreatitis (13, 14). In addition, we excluded trials in which the early group was fed more

Figure 2. Comparison of length of hospital stay for patients with acute pancreatitis randomly assigned to early versus delayed feeding.



Length of stay reported in studies as mean and SD, or as median and IQR, range, or IQR and range. IQR = interquartile range; NR = not reported. * IQR not reported, so only median and range are shown. Length of stay in the delayed group ranged from 5 to 94 d.

than 48 hours after hospitalization in an attempt to standardize the definition of "early," because many of the early groups in excluded studies and other reviews are delayed by modern standards.

Our study should be interpreted in the context of its limitations. First, we were unable to conduct a meta-analysis due to clinical heterogeneity across studies. As such, insights into the precise magnitude of benefits among feeding strategies are limited. Second, results were constrained by reported outcomes, which were highly variable, particularly readmission rates. Third, because only 11 randomized trials met inclusion criteria and many studies were small, we had limited power to detect rare outcomes. Fourth, some patient groups were excluded from the included trials; thus, our findings cannot be generalized to these populations. Fifth, 3 trials were reported in abstract form only and thus have not undergone full peer review. Sixth, only 4 trials were assessed as having low risk of bias. Finally, using length of hospital stay as an outcome has limitations, including a complex relationship with mortality, and it must be interpreted in the context of other clinical outcomes.

Despite these limitations, our study has important implications. First, we believe our results should encourage clinicians to consider early feeding for patients with pancreatitis. This approach may lead to fewer symptoms without harm. In an increasingly cost-conscious environment, early feeding may be an effective strategy to decrease length of hospital stay. Second, our findings differ from 2013 U.S. guidelines for pancreatitis that recommend waiting to start feeding until "inflammatory markers are improving" (14) or "abdominal pain has resolved" (13). With 3 randomized clinical trials (21, 30, 31) not included in previous reviews (5, 11–14, 18, 44, 45), our review suggests that waiting to initiate enteral nutrition may not be necessary and can inform new policy in this regard.

In conclusion, early feeding for patients with mild to moderate acute pancreatitis does not seem to be associated with adverse events and may reduce length of hospital stay and gastrointestinal symptoms. However, limitations, including the sample size of included studies, variation in outcomes and protocols, and unclear or high risk of bias, limit generalizability. Further

studies evaluating the optimal timing and method of feeding are necessary.

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References

1. **Peery AF, Crockett SD, Barritt AS, Dellon ES, Eluri S, Gangarosa LM, et al.** Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology. 2015;149:1731-41. [PMID: 26327134] doi:10.1053/j.gastro.2015.08.045
2. **Yadav D, Lowenfels AB.** Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006;33:323-30. [PMID: 17079934]
3. **Harrison TR.** Principles of Internal Medicine. Philadelphia: Blakiston; 1950.
4. **Ammori BJ.** Role of the gut in the course of severe acute pancreatitis. Pancreas. 2003;26:122-9. [PMID: 12604908]
5. **Ol h A, Romics L Jr.** Enteral nutrition in acute pancreatitis: a review of the current evidence. World J Gastroenterol. 2014;20:16123-31. [PMID: 25473164] doi:10.3748/wjg.v20.i43.16123
6. **Li W, Qiu F, Tong Z, Wang X, Yu W, Li N, et al.** The effect of early vs. delayed enteral nutrition on gastrointestinal and immune function of the patients with severe acute pancreatitis. A randomized controlled clinical trial. Pancreatology. 2010;10:264.
7. **Jiang K, Chen XZ, Xia Q, Tang WF, Wang L.** Early nasogastric enteral nutrition for severe acute pancreatitis: a systematic review. World J Gastroenterol. 2007;13:5253-60. [PMID: 17876897]
8. **McClave SA, Chang WK, Dhaliwal R, Heyland DK.** Nutrition support in acute pancreatitis: a systematic review of the literature. JPEN J Parenter Enteral Nutr. 2006;30:143-56. [PMID: 16517959]
9. **Al Samaraee A, McCallum IJ, Coyne PE, Seymour K.** Nutritional strategies in severe acute pancreatitis: a systematic review of the evidence. Surgeon. 2010;8:105-10. [PMID: 20303893] doi:10.1016/j.surge.2009.10.006
10. **Petrov MS, Pylypchuk RD, Emelyanov NV.** Systematic review: nutritional support in acute pancreatitis. Aliment Pharmacol Ther. 2008;28:704-12. [PMID: 19145726]
11. **M rta K, Farkas N, Szab I, Ill s A, Vincze , P r G, et al.** Meta-analysis of early nutrition: the benefits of enteral feeding compared to a nil per os diet not only in severe, but also in mild and moderate acute pancreatitis. Int J Mol Sci. 2016;17. [PMID: 27775609]
12. **Horibe M, Nishizawa T, Suzuki H, Minami K, Yahagi N, Iwasaki E, et al.** Timing of oral refeeding in acute pancreatitis: a systematic review and meta-analysis. United European Gastroenterol J. 2016;4:725-32.
13. **Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology.** American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400-15. [PMID: 23896955] doi:10.1038/ajg.2013.218
14. **Working Group IAP/APA Acute Pancreatitis Guidelines.** IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13:e1-15. [PMID: 24054878] doi:10.1016/j.pan.2013.07.063
15. **Dua MM, Worhunsky DJ, Tran TB, Rumma RT, Poultsides GA, Norton JA, et al.** Severe acute pancreatitis in the community: confusion reigns. J Surg Res. 2015;199:44-50. [PMID: 25972313] doi:10.1016/j.jss.2015.04.054
16. **Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedrich JO, Nathens A, et al.** Compliance with evidence-based guidelines in acute pancreatitis: an audit of practices in University of Toronto hospitals. J Gastrointest Surg. 2016;20:392-400. [PMID: 26621675] doi:10.1007/s11605-015-3023-9
17. **Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group.** Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006-12. [PMID: 19631508] doi:10.1016/j.jclinepi.2009.06.005
18. **Li JY, Yu T, Chen GC, Yuan YH, Zhong W, Zhao LN, et al.** Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: a meta-analysis. PLoS One. 2013;8:e64926. [PMID: 23762266] doi:10.1371/journal.pone.0064926
19. **Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup.** Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637. [PMID: 23353941] doi:10.1097/CCM.0b013e31827e83af
20. **Higgins JPT, Green S, eds.** Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1. The Cochrane Collaboration. Updated March 2011]. Accessed at www.cochrane-handbook.org on 2 July 2015.
21. **Badalov NL, Mehta Z, Satyavolu H, Shah T, Li JJ, Baradarian R, et al.** Early oral feeding in mild acute pancreatitis: a randomized prospective trial. Am J Gastroenterol. 2007;102:S192.
22. **Powell JJ, Murchison JT, Fearon KC, Ross JA, Siriwardena AK.** Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. Br J Surg. 2000;87:1375-81. [PMID: 11044164]
23. **Wu D, Ding Y, Deng B, Xiao W, Wu J, Yan Z, et al.** Clinical case-control study of early enteral nutrition through three lumen gas-

trojejunal tube in severe acute pancreatitis. Parenteral & Enteral Nutrition. 2008;15:285-7.
24. **Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al; Dutch Pancreatitis Study Group.** Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med. 2014;371:1983-93. [PMID: 25409371] doi:10.1056/NEJMoa1404393
25. **Stimac D, Poropat G, Hauser G, Licul V, Franjic N, Valkovic Zujic P, et al.** Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: a randomized clinical trial. Pancreatology. 2016;16:523-8. [PMID: 27107634] doi:10.1016/j.pan.2016.04.003
26. **Eckerwall GE, Tingstedt BB, Bergenzaun PE, Andersson RG.** Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery—a randomized clinical study. Clin Nutr. 2007;26:758-63. [PMID: 17719703]
27. **Teich N, Aghdassi A, Fischer J, Walz B, Caca K, Wallochny T, et al.** Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. Pancreas. 2010;39:1088-92. [PMID: 20357692] doi:10.1097/MPA.0b013e3181d3ce05
28. **Petrov MS, McIlroy K, Grayson L, Phillips AR, Windsor JA.** Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. Clin Nutr. 2013;32:697-703. [PMID: 23340042] doi:10.1016/j.clnu.2012.12.011
29. **Lari o-Noia J, Lindkvist B, Iglesias-Garc a J, Seijo-R os S, Iglesias-Canle J, Dom nguez-Mu oz JE.** Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. Pancreatology. 2014;14:167-73. [PMID: 24854611] doi:10.1016/j.pan.2014.02.008
30. **Kurti F, Xinxo S, Shpata V, Kavaja G, Duni A, Basho J.** Role of enteral feeding in mild to moderate acute pancreatitis. Pancreatology. 2015;15:S62.
31. **Karabulut U, Koyuncu MB, Sezgin O, Ucbilek E, Aydin MK, Altintas E.** Early oral feeding and selection of initial diet in mild acute pancreatitis. Gastroenterology. 2014;146:S621.
32. **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;35:2018-27. [PMID: 19777207] doi:10.1007/s00134-009-1664-4
33. **Buchman AL, Moukarzel AA, Bhuta S, Belle M, Ament ME, Eckhert CD, et al.** Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. JPEN J Parenter Enteral Nutr. 1995;19:453-60. [PMID: 8748359]
34. **Flint RS, Windsor JA.** The role of the intestine in the pathophysiology and management of severe acute pancreatitis. HPB (Oxford). 2003;5:69-85. [PMID: 18332961] doi:10.1080/13651820310001108
35. **Wu Y, Kudsk KA, DeWitt RC, Tolley EA, Li J.** Route and type of nutrition influence IgA-mediating intestinal cytokines. Ann Surg. 1999;229:662-7. [PMID: 10235524]
36. **Wereszczynska-Siemiatkowska U, Swidnicka-Siergiejko A, Siemiatkowski A, Dabrowski A.** Early enteral nutrition is superior to delayed enteral nutrition for the prevention of infected necrosis and mortality in acute pancreatitis. Pancreas. 2013;42:640-6. [PMID: 23508012] doi:10.1097/MPA.0b013e318271bb61
37. **Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW.** Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. Am J Respir Crit Care Med. 1995;152:1545-8. [PMID: 7582291]
38. **Hernandez G, Velasco N, Wainstein C, Castillo L, Bugedo G, Maiz A, et al.** Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care. 1999;14:73-7. [PMID: 10382787]
39. **McClure RJ, Newell SJ.** Randomised controlled study of clinical outcome following trophic feeding. Arch Dis Child Fetal Neonatal Ed. 2000;82:F29-33. [PMID: 10634838]
40. **McClave SA, Martindale RG, Rice TW, Heyland DK.** Feeding the critically ill patient. Crit Care Med. 2014;42:2600-10. [PMID: 25251763] doi:10.1097/CCM.0000000000000654
41. **Bakker OJ, van Brunschot S, Farre A, Johnson CD, Kalfarentzos F, Louie BE, et al.** Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomised trials. Pancreatology. 2014;14:340-6. [PMID: 25128270] doi:10.1016/j.pan.2014.07.008
42. **Zhao XL, Zhu SF, Xue GJ, Li J, Liu YL, Wan MH, et al.** Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. Nutrition. 2015;31:171-5. [PMID: 25441594] doi:10.1016/j.nut.2014.07.002
43. **Li J, Xue GJ, Liu YL, Javed MA, Zhao XL, Wan MH, et al.** Early oral refeeding wisdom in patients with mild acute pancreatitis. Pancreas. 2013;42:88-91. [PMID: 22836861] doi:10.1097/MPA.0b013e3182575fb5
44. **Ol h A, Romics L Jr.** Evidence-based use of enteral nutrition in acute pancreatitis. Langenbecks Arch Surg. 2010;395:309-16. [PMID: 20309576] doi:10.1007/s00423-010-0631-4
45. **Li X, Ma F, Jia K.** Early enteral nutrition within 24 hours or between 24 and 72 hours for acute pancreatitis: evidence based on 12 RCTs. Med Sci Monit. 2014;20:2327-35. [PMID: 25399541] doi:10.12659/MSM.892770

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Appendix: Search Strategy

Updated 25 March 2015

Reference numbers: (search results > imported with duplicates removed by EndNote > count after manual deduplication)

Ovid MEDLINE (241 > 237 > 235)

exp pancreatitis/ or "acute pancreatitis".mp. or pancreatitis.mp.

AND

(fast* or (pancreas adj5 rest*) or "nil by mouth" or "nil per os" or (delayed adj5 (feed* or nourish* or nutrition))).mp.

OR

exp eating/ or exp enteral nutrition/ or "enteral nutrition".mp. or ((enteral or oral or nasogastric or nasojejunal) and (nutrition or feed*)).mp. or (nourish* or diet* or feed or feeds or feeding or eat* or refeed*).mp.

AND

randomized controlled trial.pt. or exp randomized controlled trials as topic/ or (randomi?ed adj5 (subject* or participant* or trial*)).mp. or (double adj2 blind*).mp.

Updated 13 Nov 2015 with py = 2014-2016 OR ed = 20150325-20161231: 39>35> 35

Updated 5 Feb 2016 with py = 2015-2016 = 36>15>14

Updated 8 July 2016 with py = 2016 = 10 > 8

Updated 10 Oct 2016 (including epub ahead of print) with py = 2016: 10 > 10

Updated 6 Jan 2017 with py = 2016-2017: 21 > 15

EMBASE (433 > 332 > 281)

'pancreatitis'/de OR 'acute pancreatitis'/de OR pancreatitis:ab,ti

AND

'diet restriction'/exp OR 'artificial feeding'/exp OR 'eating'/exp OR 'nil by mouth':ab,ti OR 'nil per os':ab,ti OR delayed NEAR/5 (feed* OR nourish* OR nutrition) OR (enteral OR oral OR enteric OR nasogastric OR nasojejunal) NEAR/2 (nutrition OR feed*) OR nourish*:ab,ti OR feed:ab,ti OR feeds:ab,ti OR feeding:ab,ti OR eat*:ab,ti OR refeed*:ab,ti OR fast* OR pancrea* NEAR/5 rest*

AND

randomi?ed NEXT/1 ('controlled trial' OR trial*) OR randomi?ed NEAR/5 (subject* OR participant* OR trial*) OR double NEAR/2 blind*

Updated 13 Nov 2015 with start date 25/3/2015 – present: 40/32/28

Updated 5 Feb 2016 with start date 1/11/2015 – 19/2/2016: 490>17>14

Updated 8 July 2016 with start date 19/2/2016 – 22/7/2016: 510 > 29 > 24 > 21

Updated 10 Oct with start date 1/7/2016 – 10/10/2016: 14 > 8

Updated 6 Jan 2017 10/10/2016 – 01/31/2017: 14 > 13

Cochrane Library (Reviews, other Reviews, other Trials) (249 > 239 > 60)

Pancreatitis

AND

fast* OR (pancrea* NEAR/3 rest*) OR "nil by mouth" OR "nil per os" OR (delayed NEXT/5 (feed* OR nourish* OR nutrition)) OR (enteral OR enteric) NEXT nutrition OR ((enteral OR oral OR nasogastric OR nasojejunal) AND (nutrition OR feed*)) OR nourish* OR diet* OR feed OR feeds OR feeding OR eat* OR refeed*

AND

randomi?ed NEAR/3 ("controlled trial" OR "controlled trials" OR trial* or subject* OR participant*) OR double NEAR/2 blind*

Updated 13 Nov 2015 with publication year 2015 - : 17>17>7

Updated 5 Feb 2016 with publication year 2015 – 2016: 23 >15

Updated 8 July 2016 with publication year 2016 = 5 > 3

Updated 10 October 2016 with publication year 2016 = 12 > 10

Updated 6 January 2017 with publication year 2016/17: 28 > 23

CINAHL (35 > 7)

(MH "Pancreatitis+") OR TI pancreatitis OR AB pancreatitis

AND

((MH "Enteral Nutrition") OR (MH "Eating")) OR TI ((fast* OR (pancrea* N5 rest*)) OR "nil by mouth" OR "nil per os" OR (delayed N5 (feed* or nourish* or nutrition)) OR ((enteral OR enteric) W2 nutrition) OR ((enteral OR oral OR nasogastric OR nasojejunal) AND nutrition OR feed*)) OR nouris* OR diet* OR feed OR feeds OR feeding OR eat* OR refeed*) OR AB ((fast* OR (pancrea* N5 rest*)) OR "nil by mouth" OR "nil per os" OR (delayed N5 (feed* or nourish* or nutrition)) OR ((enteral OR enteric) W2 nutrition) OR ((enteral OR oral OR nasogastric OR nasojejunal) AND nutrition OR feed*)) OR nouris* OR diet* OR feed OR feeds OR feeding OR eat* OR refeed*)

AND

TI (randomi?ed W2 ("controlled trial" OR "controlled trials") OR (randomi?ed N5 (trial* OR subject* OR participant*)) OR double N2 blind*) OR AB (randomi?ed W2 ("controlled trial" OR "controlled trials") OR (randomi?ed N5 (trial* OR subject* OR participant*)) OR double N2 blind*)

Updated 13 Nov 2015 with Publication year March 2015 - : 3>3>2

Updated 5 Feb 2016 with DT 2015 OR DT 2016: 5>4>3

Updated 8 July 2016 with DT 2016: 4 – all duplicates

Updated 10 Oct 2016 with DT 2016: 4 – all duplicates

Updated 6 Jan 2017: 4 – all duplicates

WoS (CPCI-S and SCI_Expanded) (447 > 333 > 294)

Pancreatitis

AND

fast* OR (pancreas AND rest*) OR "enteral nutrition" OR "enteric nutrition" OR "delayed feeding" OR (delay* AND (nutrition OR nourish*)) OR ((enteral OR oral OR nasogastric OR nasojejunal) AND (nutrition OR feed*)) OR nourish* OR diet* OR feed OR feeds OR feeding OR eat* OR refeed*

AND

"randomized controlled trial" OR "randomised controlled trial" OR ((randomized OR randomised) AND (trial* OR subject* OR participant)) OR (double AND blind*)

Updated 13 Nov 2015 with 2015 - : 31>23>20

Updated 5 Feb 2016 with 2015-2016: 35>27>22

Updated 8 July 2016 with 2016 – 2016: 23 > 20 > 17

Updated 8 July 2016 with 2016 – 2016: 31 > 22

Updated 6 Jan 2017 with 2016 – 2017: 36 > 30 > 25

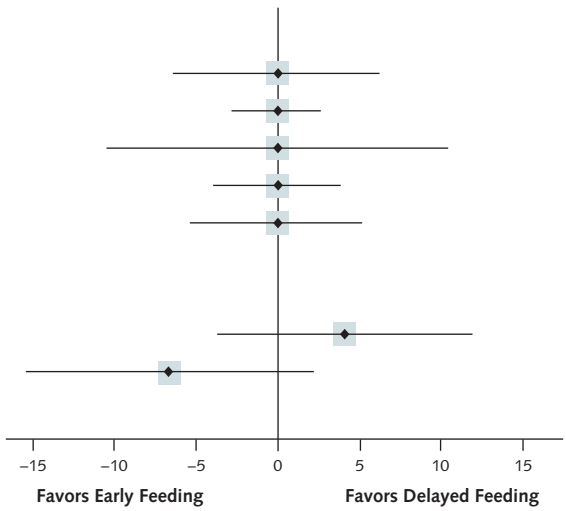
Appendix Table. Risk of Bias in Studies Comparing Early Versus Delayed Feeding in Patients With Acute Pancreatitis

Study, Year (Reference)	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Source of Bias	Summary Bias
Mild/moderate pancreatitis							
Badalov et al, 2007 (21)	Unclear	Unclear	Low	Unclear	Unclear	Not yet peer-reviewed	Unclear
Eckerwall et al, 2007 (26)	Low	Low	Low	Low	Low	NA	Low
Teich et al, 2010 (27)	Low	Low	Low	High	Low	Asymmetrical dropout	High
Petrov et al, 2013 (28)	Low	Low	Low	Low	Low	Stopped early because of formal stopping rule	Low
Karabulut et al, 2014 (31)	Unclear	Unclear	Low	Unclear	Unclear	Not yet peer-reviewed	Unclear
Larĩno-Noia et al, 2014 (29)	Low	Low	Low	Low	Low	NA	Low
Kurti et al, 2015 (30)	Unclear	Unclear	Low	Unclear	Unclear	Not yet peer-reviewed	Unclear
Severe pancreatitis							
Powell et al, 2000 (22)	Unclear	Unclear	Low	High	Low	Not well-described protocol	High
Wu et al, 2008 (23)	Low	Low	Low	Unclear	Unclear	Unclear; outdated standard of care	Unclear
Bakker et al, 2014 (24)	Low	Low	Low	Low	Low	High mortality that could affect LOS	Low
Stimac et al, 2016 (25)	Low	Low	Low	Low	Unclear	High mortality that could affect LOS	Unclear

LOS = length of stay; NA = not applicable.

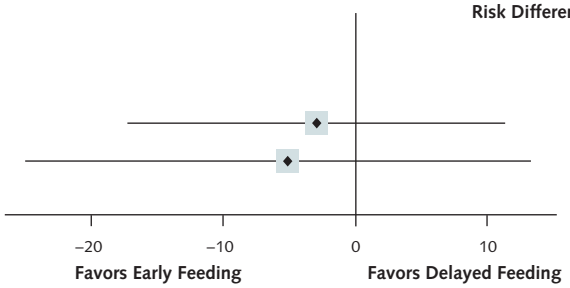
Appendix Figure 1. Risk difference in mortality in studies comparing early (≤48 h after hospitalization) versus delayed (>48 h after hospitalization) feeding in patients with acute pancreatitis.

Study, Year (Reference)	Sample Size, *n*		Died, *n* (%)		Risk Difference (95% CI), %
	Early Feeding	Delayed Feeding	Early Feeding	Delayed Feeding	
Mild/Moderate					
Eckerwall et al, 2007 (26)	29	30	0 (0)	0 (0)	0 (−6 to 6)
Teich et al, 2010 (27)	69	74	0 (0)	0 (0)	0 (−3 to 3)
Petrov et al, 2013 (28)	17	18	0 (0)	0 (0)	0 (−10 to 10)
Karabulut et al, 2014 (31)	49	49	0 (0)	0 (0)	0 (−4 to 4)
Lariño-Noia et al, 2014 (29)	37	35	0 (0)	0 (0)	0 (−5 to 5)
Severe					
Bakker et al, 2014 (24)	101	104	11 (10.9)	7 (6.7)	4 (−4 to 12)
Stimac et al, 2016 (25)	107	107	10 (9.3)	17 (15.9)	−7 (15 to 2)



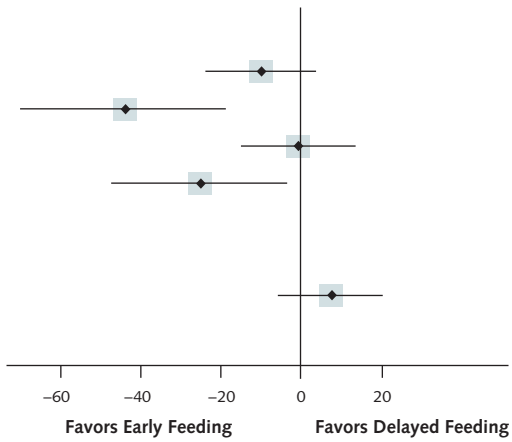
Appendix Figure 2. Risk difference in rehospitalization in studies comparing early (≤48 h after hospitalization) versus delayed (>48 h after hospitalization) feeding in patients with acute pancreatitis.

Study, Year (Reference)	Sample Size, *n*		Readmitted, *n* (%)		Risk Difference (95% CI), %
	Early Feeding	Delayed Feeding	Early Feeding	Delayed Feeding	
Mild/Moderate					
Eckerwall et al, 2007 (26)	29	30	2 (6.9)	3 (10.0)	−3 (−17 to 11)
Petrov et al, 2013 (28)	17	18	1 (5.9)	2 (11.1)	−5 (−24 to 13)



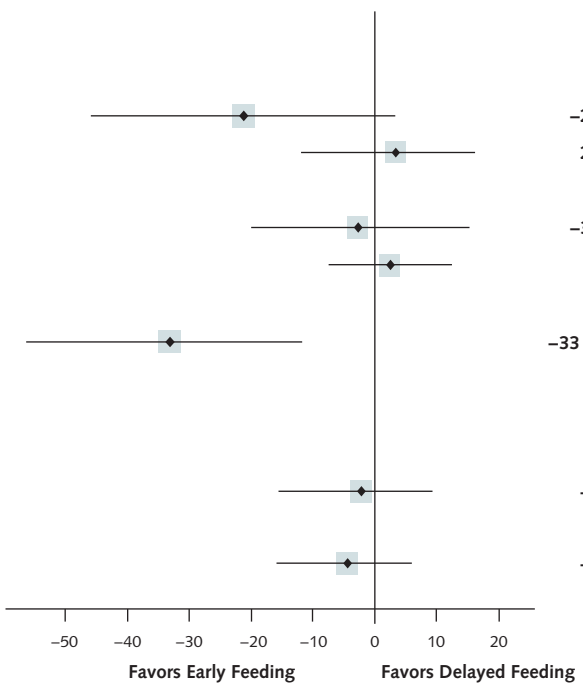
Appendix Figure 3. Risk difference in feeding intolerance in studies comparing early (≤48 h after hospitalization) versus delayed (>48 h after hospitalization) feeding in patients with acute pancreatitis.

Study, Year (Reference)	Sample Size, *n*		Intolerance, *n* (%)		Risk Difference (95% CI), %
	Early Feeding	Delayed Feeding	Early Feeding	Delayed Feeding	
Mild/Moderate					
Eckerwall et al, 2007 (26)	29	30	1 (3.4)	4 (13.3)	−10 (−24 to 4)
Petrov et al, 2013 (28)	17	18	1 (5.9)	9 (50.0)	−44 (−70 to −18)
Lariño-Noia et al, 2014 (29)	37	35	4 (10.8)	4 (11.4)	−1 (−15 to 14)
Kurti et al, 2015 (30)	21	20	1 (4.8)	6 (30.0)	−25 (−47 to −3)
Severe					
Stimac et al, 2016 (25)	107	107	65 (60.7)	57 (53.3)	7 (−6 to 21)



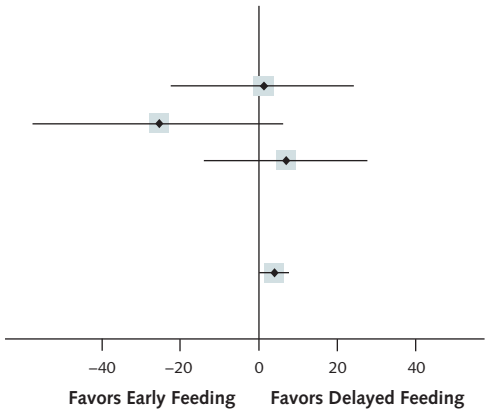
Appendix Figure 4. Risk difference in nausea and vomiting in studies comparing early (≤48 h after hospitalization) versus delayed (>48 h after hospitalization) feeding in patients with acute pancreatitis.

Study, Year (Reference)	Sample Size, *n*		Nausea/Vomiting, *n* (%)		Risk Difference (95% CI), %
	Early Feeding	Delayed Feeding	Early Feeding	Delayed Feeding	
Mild/Moderate					
Nausea					
Eckerwall et al, 2007 (26)	29	30	9 (31.0)	16 (53.3)	−22 (−47 to 2)
Lariño-Noia et al, 2014 (29)	37	35	4 (10.8)	3 (8.6)	2 (−11 to 16)
Vomiting					
Eckerwall et al, 2007 (26)	29	30	4 (13.8)	5 (16.7)	−3 (−21 to 15)
Lariño-Noia et al, 2014 (29)	37	35	2 (5.4)	1 (2.9)	3 (−7 to 12)
Nausea or vomiting					
Petrov et al, 2013 (28)	17	18	0 (0)	6 (33.3)	−33 (−56 to −11)
Severe					
Nausea					
Bakker et al, 2014 (24)	101	104	32 (31.7)	37 (35.6)	−4 (−17 to 9)
Vomiting					
Bakker et al, 2014 (24)	101	104	19 (18.8)	26 (25.0)	−6 (−17 to 5)



Appendix Figure 5. Risk difference in recurrent abdominal pain in studies comparing early (≤48 h after hospitalization) versus delayed (>48 h after hospitalization) feeding in patients with acute pancreatitis.

Study, Year (Reference)	Sample Size, *n*		Pain, *n* (%)		Risk Difference (95% CI), %
	Early Feeding	Delayed Feeding	Early Feeding	Delayed Feeding	
Mild/Moderate					
Eckerwall et al, 2007 (26)	29	30	9 (31.0)	9 (30.0)	1 (–22 to 24)
Petrov et al, 2013 (28)	17	18	7 (41.2)	12 (66.7)	–25 (–57 to 6)
Lariño-Noia et al, 2014 (29)	37	35	12 (32.4)	9 (25.7)	7 (–14 to 28)
Severe					
Stimac et al, 2016 (25)	107	107	4 (3.7)	0 (0.0)	4 (0 to 8)



Appendix Figure 6. Risk difference in necrotizing pancreatitis in studies comparing early (≤48 h after hospitalization) versus delayed (>48 h after hospitalization) feeding in patients with acute pancreatitis.

Study, Year (Reference)	Sample Size, *n*		Necrosis, *n* (%)		Risk Difference (95% CI), %
	Early Feeding	Delayed Feeding	Early Feeding	Delayed Feeding	
Mild/Moderate					
Eckerwall et al, 2007 (26)	29	30	0 (0)	0 (0)	0 (–6 to 6)
Severe					
Bakker et al, 2014 (24)	101	104	64 (63.4)	65 (62.5)	1 (–12 to 14)
Stimac et al, 2016 (25)	107	107	37 (34.6)	33 (30.8)	4 (–9 to 16)