A systematic review on the timing of artificial nutrition in acute pancreatitis
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CRD summary
The authors found that enteral nutrition was superior to parenteral nutrition for reducing multiple organ failure, pancreatic infectious complications and mortality associated with acute pancreatitis. The degree of benefit may depend upon when nutrition was initiated. Due to the questionable quality of the primary studies and the use of indirect comparisons for some analyses, these conclusions may not be reliable.

Authors' objectives
To compare the effectiveness of enteral versus parenteral nutrition administered at different time points to patients with acute pancreatitis.

Searching
Cochrane Central register of Controlled Trials (CENTRAL), MEDLINE and Science Citation Index were searched for studies from 1950 to March 2008. Search terms were reported. Abstracts of major gastroenterology meetings and reference lists of relevant studies and reviews were checked. The search was limited to studies in English, French, German, Russian, Spanish or Dutch.

Study selection
Randomised controlled trials (RCTs) of enteral versus parenteral nutrition for acute pancreatitis were eligible for inclusion provided they reported the timing of initiation of nutrition. Studies needed to report at least two of the following outcomes: multiple organ failure; pancreatic infectious complications; and mortality.

Participants in most included studies had severe pancreatitis; some studies included participants with either mild or severe pancreatitis. Studies initiated nutrition at widely differing time points, which ranged from under six to over 96 hours post admission. The mean duration of feeding ranged from two to 35 days for enteral nutrition and from three to 33 days for parenteral nutrition (where stated). Most studies did not report criteria for maximum time since symptom onset; where reported, this was stated as less than 48 hours or less than 72 hours.

Potentially relevant studies were assessed independently by two reviewers. Differences were resolved by consensus.

Assessment of study quality
The Jadad scale was used to assess the quality of reported randomisation, double-blinding and management of withdrawals and dropouts in the included studies. Each study was awarded a score of up to 5 points; a score over 2 was taken to indicate good quality. The validity assessment was conducted independently by two reviewers.

Data extraction
Risk ratios (RRs) were calculated from the numbers of events in the enteral and parenteral nutrition groups of each study, with 95% confidence intervals (CIs). Data were categorised as either early or delayed, according to the timing of initiation of nutrition. Two different thresholds were used: within/later than 24 hours from admission; and within/later than 48 hours from admission. Data were extracted independently by two reviewers.

Methods of synthesis
To compare types of nutrition, studies were combined to calculate pooled risk ratios and 95% CIs using a random-effects model. The $I^2$ test and $\chi^2$ test were used to assess statistical heterogeneity, with values of over 25% and under 0.1 (respectively) taken to denote statistical significance. Publication bias was assessed by funnel plots with Egger's test. A subgroup analysis was conducted of studies where all participants had severe pancreatitis. To compare timing of initiation of nutrition, analyses were stratified into early and delayed groups. The interaction effect between the groups was estimated as a ratio of their risk ratios and used the test of interaction to calculate statistical significance.
Results of the review
Eleven RCTs were included in the review (n=451, range 17 to 89). Six studies were considered good quality. All studies reported randomisation, but three did not describe how treatment was assigned. Ten described withdrawals and dropouts. None were double-blinded.

Enteral versus parenteral nutrition among patients with mild or severe pancreatitis: Enteral nutrition started within 48 hours of admission was associated with significantly less risk than parenteral nutrition of multiple organ failure (RR 0.44, 95% CI 0.23 to 0.84; three RCTs), pancreatic infectious complications (RR 0.46, 95% CI 0.27 to 0.77; five RCTs) or mortality (RR 0.46, 95% CI 0.20 to 0.99; five RCTs). Findings were similar when nutrition was initiated within 24 hours of admission (four RCTs). When nutrition was initiated more than 48 hours after admission (four RCTs), the difference between the groups was no longer statistically significant. Statistical heterogeneity was low or absent for these analyses.

Early versus delayed nutrition among patients with mild or severe pancreatitis: There was no statistically significant interaction between early versus delayed groups for any outcome at either time threshold. There was a trend for greater risk reduction associated with delayed nutrition for the outcome of pancreatic infectious complications, but not for other outcomes.

The results of the subgroup analysis were reported.

Authors’ conclusions
Enteral nutrition was superior to parenteral nutrition for reducing multiple organ failure, pancreatic infectious complications and mortality associated with acute pancreatitis. The degree of benefit may have depended upon when nutrition was initiated.

CRD commentary
The dual objectives of the review (to compare types and timing of nutrition) made the findings rather difficult to interpret, especially as there were no trials that directly compared timing of nutrition. Relevant sources were searched for studies without restriction by publication status, but the restriction by language meant that some studies may have been missed. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently involved in study selection, validity assessment and data extraction. Relevant aspects of quality were considered, although no details were provided on some important components of validity (such as withdrawal rates). Appropriate statistical techniques were used to pool study data to compare types of nutrition and to assess for heterogeneity and publication bias. However, few results of individual studies were presented and the findings of the tests for publication bias were not reported. Most studies were very small and many were of questionable quality; as the authors noted, the duration of symptoms was frequently unknown, and in some studies patients who died early in the course of the disease or needed surgical intervention were excluded. The findings regarding the timing of nutrition were of doubtful validity in view of their indirect nature and high potential for confounding. Due to the small size and questionable quality of the primary studies and the use of indirect comparisons for some analyses, the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that enteral nutrition was of clear benefit to patients with acute pancreatitis if initiated within 24 or 48 hours of admission, but of less obvious benefit in patients where initiation of nutrition was delayed.

Research: The authors stated that an RCT was required to compare early versus delayed initiation of feeding in patients with acute pancreatitis.

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