Artificial nutrition is an inherent part of management in acute pancreatitis. However, there is no consensus regarding the optimal time of the commencement of feeding in these patients. Our aim was to compare the effect of enteral v. parenteral nutrition with regard to the time points when they were administered in the randomised controlled trials. The search was undertaken in the Cochrane Central Register of Controlled Trials, MEDLINE and Science Citation Index as well as in the proceedings of major gastroenterology meetings. The summary estimate of the effect associated with artificial nutrition was calculated using a random-effects model and presented as a risk ratio (RR) and 95% CI. A total of eleven randomised controlled trials were included. When started within 48 h of admission, enteral nutrition, in comparison with parenteral nutrition, resulted in a statistically significant reduction in the risks of multiple organ failure (RR 0·44; 95% CI 0·23, 0·84), pancreatic infectious complications (RR 0·46; 95% CI 0·27, 0·77) and mortality (RR 0·46; 95% CI 0·20, 0·99). After 48 h of admission, enteral nutrition, in comparison with parenteral nutrition, did not result in a statistically significant reduction in the risks of multiple organ failure (RR 0·73; 95% CI 0·33, 1·63), pancreatic infectious complications (RR 0·31; 95% CI 0·07, 1·34) and mortality (RR 0·67; 95% CI 0·22, 2·10). Enteral nutrition is more effective than parenteral nutrition in reducing the risk of multiple organ failure, pancreatic infectious complications and mortality in patients with acute pancreatitis. The magnitude of these benefits may depend on the timing of the commencement of nutrition.

Artificial nutrition has been regarded as an important component in the treatment of patients with acute pancreatitis(1–3). However, while parenteral nutrition had a major weight in artificial nutrition during the 1970s–1990s, the last decade was characterised by a gradual shift in nutritional management towards enteral nutrition. Three systematic reviews, which incorporated the data from available randomised controlled trials (RCT) on enteral v. parenteral nutrition in acute pancreatitis, have consistently confirmed this change and have shown a statistically significant reduction of infectious complications with the use of enteral nutrition(4–6). Moreover, a recent meta-analysis, confined to RCT on patients with severe acute pancreatitis, revealed a significantly reduced mortality in patients received enteral over parenteral nutrition(7).

At the same time, the mechanism of such a beneficial effect of enteral nutrition is not entirely understandable(8,9). At least in part, the timing of nutrition might have an influence on the results observed. In general, it is supposed that enteral nutrition contributes to the maintenance of the intestinal barrier function and may prevent bacterial translocation from the lumen(10,11). Thereby, intuitively it seems logical to commence enteral nutrition early in the course of acute pancreatitis(2,12). However, whereas some authors advocate the early start of nutrition within the hours after hospital admission(12–14), others prefer a wait-and-see policy, when the commencement of enteral feeding may be postponed for up to 17 d after admission to hospital(15,17). So, until now the optimal time frameworks for the initiation of feeding in patients with acute pancreatitis have not yet been investigated.

Therefore, we aimed at conducting a systematic review of RCT on enteral v. parenteral nutrition in patients with acute pancreatitis to define whether the time of the commencement of nutrition has an influence on the risk of clinically meaningful outcomes such as multiple organ failure, pancreatic infectious complications and mortality.

**Methods**

**Study selection**

We performed an electronic search for publications between 1950 and 1 March 2008, using the Cochrane Central Register of Controlled Trials, MEDLINE and Science Citation Index. The search was restricted to human studies that were published in English, French, German, Russian, Spanish or Dutch.
The terms used for the search in the Cochrane Central Register of Controlled Trials and Science Citation Index were: ‘acute pancreatitis’ and ‘enteral nutrition’ or ‘parenteral nutrition’ and ‘randomised trial’. The terms used for the search in MEDLINE were: ‘pancreatitis’ (medical subject heading (MeSH)) and ‘enteral nutrition’ (MeSH) or ‘parenteral nutrition’ (MeSH) or ‘parenteral nutrition, total’ (MeSH) and ‘randomised controlled trials’ (publication type). Reference lists of all available published RCT and reviews on nutrition in acute pancreatitis were cross-checked manually to ensure that all applicable papers were included. Additionally, the abstracts of major gastroenterology congresses were also searched manually.

Each potentially relevant RCT was assessed for inclusion independently by two reviewers. Differences in opinion between the reviewers were resolved by consensus. Accepted interventions included enteral nutrition v. parenteral nutrition in acute pancreatitis. Only studies that reported the timing of the initiation of the nutrition protocol and the data on at least two of the three most clinically meaningful outcomes (multiple organ failure, pancreatic infectious complications and mortality) were considered.

Data extraction and quality assessment

Two reviewers, by means of a standardised data collection form, independently extracted general trial information, data on the study quality, details of nutrition protocols, including the timing of feeding start, and outcome data. Outcome variables included in the meta-analysis were: multiple organ failure, pancreatic infectious complications and mortality. The Jadad scale was used to assess the following aspects of the study quality: randomisation, double-blinding, withdrawals and drop-outs (minimum total score 0, maximum total score 5). An RCT with a score higher than 2 was considered as an RCT of good quality.

Statistical analysis

Analyses were done using the computer program Review Manager (version 4.2 for Windows; The Nordic Cochrane Centre, The Cochrane Collaboration, 2003, Copenhagen, Denmark). Pooled risk ratios (RR) and 95 % CI were calculated using a random-effects model. RR values of <1.0 represented an advantage for the enteral nutrition group compared with the parenteral nutrition group. The $I^2$ test and $\chi^2$ test were used for the evaluation of statistical heterogeneity between included trials. A value of the $I^2$ measure more than 25 % and $P$ value of the $\chi^2$ test lower than 0.1 were considered to denote the presence of statistically significant heterogeneity between included RCT. Publication bias was assessed by the funnel plot method of Egger’s test.

Predefined stratified analyses were performed to evaluate the difference in RR between trials on early v. delayed nutrition. The time of nutrition commencement in each RCT was applied to the certain time points (24 h and 48 h after admission) and the corresponding study was assigned to either early or delayed group with regard to that time point. The estimated interaction effect was calculated as a ratio of RR for early and delayed nutrition. The significance of this effect was assessed by using the test of interaction. $P$ values less than 0.05 were considered to be significant.

Results

A total of 268 reports were screened and eleven RCT met our inclusion criteria (Fig. 1). Ten reports were available as full-text papers and one was published in abstract form only. Three (27 %) trials were published before the year 2000, with regard to disease severity, seven of eleven trials incorporated solely patients with severe acute pancreatitis, whereas the patient population consisted of both patients with mild and severe acute pancreatitis in four trials. Regarding methodological quality characteristics, although all trials reported a statement on randomisation, the treatment assignment method was not described in three RCT (27 %). Double-blinding was not possible due to the nature of the interventions. The description of withdrawals and drop-outs was reported in ten (91 %) RCT. A Jadad score of higher than 2 was attributed to six (55 %) trials. The included studies comprised a total of 451 patients (214 patients received enteral nutrition and 237 patients received parenteral nutrition), ranging from seventeen to eighty-nine. Table 1 shows the study characteristics of RCT included in the systematic review. The data on study outcomes in each trial are presented in Table 2.

The nutrition protocol was initiated within 24 h of admission in four RCT and after 24 h in seven studies. With regard to this time point, the former was considered as ‘early’ nutrition and the latter as ‘delayed’ nutrition. Having applied this stratification, delayed nutrition, when compared with early nutrition, resulted in a greater risk reduction of pancreatic infectious complications (Fig. 2), but not multiple organ failure and mortality in patients with both mild and severe acute pancreatitis. The test of interaction was non-significant in all comparisons. Heterogeneity between study results in these analyses was entirely attributable to random variation ($I^2$ 0 %). When only patients from trials on severe acute pancreatitis were considered, delayed nutrition, in comparison with early nutrition, resulted in a reduction of risks for pancreatic infectious complications, multiple organ failure and mortality (Table 3). The test of interaction was non-significant. The early nutrition group had a moderate heterogeneity in regard to pancreatic complications ($I^2$ 35 %) and mortality ($I^2$ 65 %), but not multiple organ failure ($I^2$ 0 %).

The nutrition protocol was initiated within 48 h of admission in seven RCT and after 48 h in four studies. With regard to this time point, the former was considered as ‘early’ nutrition and the latter as ‘delayed’ nutrition. Having applied this stratification, delayed nutrition, when compared with early nutrition, resulted in a greater reduction of the risks for pancreatic infectious complications (Fig. 3), but not multiple organ failure and mortality in patients with both mild and severe acute pancreatitis. The test of interaction was non-significant. Heterogeneity between study results in these analyses was mainly attributable to random variation ($I^2$ 0, 0 and 21 % for multiple organ failure, pancreatic infectious complications and mortality, respectively). In trials that incorporated exclusively patients with severe...
acute pancreatitis, delayed nutrition, in comparison with early nutrition, resulted in a greater reduction of risks for pancreatic infectious complications, multiple organ failure and mortality (Table 3). The test of interaction was non-significant in all comparisons. Heterogeneity between the study results in regard to multiple organ failure, pancreatic infectious complications and mortality was low (I² 0, 0 and 23 %, respectively).

Discussion

In line with the results of previous meta-analyses (4 – 8) on enteral v. parenteral nutrition in acute pancreatitis, the present meta-analysis demonstrates the benefit of enteral nutrition in terms of risk reduction of infectious complications and mortality. For the first time, it shows a statistically significant risk reduction of multiple organ failure in patients who received enteral over parenteral nutrition. These benefits were especially pronounced in patients with severe acute pancreatitis.

Another important finding of the present meta-analysis is that the timing of nutrition in the analysed trials might affect the clinical outcomes. Namely, the difference in the efficacy between enteral and parenteral nutrition is clearly evident in patients with an early (within 24 or 48 h after admission)
The start of nutrition but less certain in patients with a delayed commencement of nutrition. Moreover, it seems that enteral nutrition started within 24 h of admission is less beneficial than enteral nutrition initiated within 48 h of admission, when compared with parenteral nutrition at corresponding time points. This may be explained if the timing of the onset of nutrition is considered in concurrence with the duration of nutrition. Even though the duration of nutrition varied between the trials, it is obvious that patients in the parenteral group were kept on a ‘nil-per-mouth’ regimen substantially longer than patients in the enteral group (whose intestine was on rest only for a short period of time from admission to the start of feeding). Thereby, the observed increasing efficacy of enteral nutrition in comparison with parenteral nutrition over the time may be due to the detrimental effect of prolonged keeping the intestine on rest in the parenterally fed group of patients with acute pancreatitis.

At the same time, the difference between the subgroup of patients with early and delayed commencement of nutrition does not reach a conventional level of significance, probably because the sample size was fairly small. Also, one should be aware that any subgroup analysis is observational in its nature and, thereby, suffers the limitations of any observational study, including possible bias through confounding. Hence, this issue should be further investigated in a study with an experimental design, i.e. an RCT on early versus delayed enteral nutrition in patients with acute pancreatitis.

Meanwhile, randomised comparisons of early versus delayed enteral nutrition have already been a subject for investigation in patients after gastrointestinal surgery and critically ill patients. In 2001, a meta-analysis, comprising of eleven RCT of early (commenced within 24 h of gastrointestinal surgery) versus delayed (commenced after 24 h of gastrointestinal surgery) enteral nutrition, showed a reduced risk of total infectious complications and reduced length of hospital stay with the use of early enteral nutrition. Recently, an updated meta-analysis, which included two additional RCT published after primary meta-analysis, demonstrated a significantly reduced mortality in patients who received enteral nutrition within 24 h of gastrointestinal surgery.

Similarly, the data from a meta-analysis of fifteen RCT in critically ill patients demonstrated the benefits of early

### Table 2. Study outcome data

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Enteral nutrition</th>
<th>Parenteral nutrition</th>
<th>Multiple organ failure</th>
<th>Enteral nutrition</th>
<th>Parenteral nutrition</th>
<th>Pancreatic infectious complications</th>
<th>Enteral nutrition</th>
<th>Parenteral nutrition</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
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<td>McClave et al. (1997)(23)</td>
<td>15</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Kalfarentzos et al. (1997)(24)</td>
<td>18</td>
<td>20</td>
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<td>Not stated</td>
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<td>4</td>
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<td>2</td>
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<td></td>
</tr>
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<td>18</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
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<td></td>
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<td>12</td>
<td>Not stated</td>
<td>Not stated</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>Ola et al. (2002)(27)</td>
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<td>2</td>
<td>5</td>
<td>5</td>
<td>13</td>
<td>2</td>
<td>4</td>
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<td>Abou-Assi et al. (2002)(28)</td>
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<td>27</td>
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<td>Not stated</td>
<td>8</td>
<td>6</td>
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<td>Gupta et al. (2003)(29)</td>
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<td>9</td>
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<tr>
<td>Louie et al. (2005)(30)</td>
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<td>4</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Eckerwall et al. (2006)(31)</td>
<td>23</td>
<td>25</td>
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<td>1</td>
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<td>Petrov et al. (2006)(32)</td>
<td>35</td>
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<td>3</td>
<td>2</td>
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<td>2</td>
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**Fig. 2.** Forest plot of risk ratios (RR) of pancreatic infectious complications in patients with both mild and severe acute pancreatitis who received enteral nutrition (EN) or parenteral nutrition (PN) within and after 24 h of admission.
(defined as the initiation of feeding within 36 h of admission to the hospital or within 36 h of surgery) over delayed (initiated after 36 h of admission to the hospital or after 36 h of surgery) enteral nutrition in terms of reduced risk of infectious complications and reduced length of hospital stay. However, a number of conflicting trials were published following this meta-analysis. In particular, in an RCT on patients with severe burns, early enteral nutrition (started within 24 h of injury) was associated with significantly lower urinary lactulose level and lactulose:mannitol ratio in comparison with delayed enteral nutrition (initiated after 48 h of injury), suggesting that an early start of feeding may decrease intestinal permeability and, consequently, prevent or attenuate bacterial translocation. At the same time, two RCT did not show a benefit of an early onset of enteral feeding. In an RCT on patients with burn injuries, Peck et al. found no benefits of early enteral nutrition (within 24 h of injury) when compared with delayed enteral nutrition (after 7 d of injury) in terms of infectious complications, mortality and length of hospital stay. The same clinical outcomes did not differ with the use of early (within 72 h of injury) vs. delayed (after 120 h of injury) enteral nutrition in an RCT on patients with acute spinal cord injury. Unfortunately, both RCT were markedly underpowered with regard to the primary end-point and, therefore, their results should be interpreted with caution.

The present systematic review has a number of limitations. First, there is no uniformity in the definition of ‘early’ enteral nutrition.

Table 3. The results of stratified meta-analysis and test of interaction

<table>
<thead>
<tr>
<th>Timing</th>
<th>Study population</th>
<th>Outcome</th>
<th>RR</th>
<th>95 % CI</th>
<th>P</th>
<th>RR</th>
<th>95 % CI</th>
<th>P</th>
<th>Estimated interaction effect</th>
<th>z</th>
<th>P</th>
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</thead>
<tbody>
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<td>24 h</td>
<td>Mild and severe acute pancreatitis</td>
<td>Multiple organ failure</td>
<td>0-44</td>
<td>0-23, 0-84</td>
<td>0-01</td>
<td>0-73</td>
<td>0-33, 1-63</td>
<td>0-45</td>
<td>0-60</td>
<td>-0-96</td>
<td>0-34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic infectious complications</td>
<td>0-47</td>
<td>0-26, 0-83</td>
<td>0-01</td>
<td>0-37</td>
<td>0-14, 0-96</td>
<td>0-04</td>
<td>1-27</td>
<td>0-39</td>
<td>0-69</td>
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<tr>
<td></td>
<td>Severe acute pancreatitis</td>
<td>Multiple organ failure</td>
<td>0-47</td>
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<td>0-84</td>
<td>0-42, 1-67</td>
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<td>0-54</td>
<td>-1-36</td>
<td>0-17</td>
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<td></td>
<td></td>
<td>Mortality</td>
<td>0-43</td>
<td>0-21, 0-88</td>
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<td>0-20</td>
<td>0-01, 3-74</td>
<td>0-28</td>
<td>2-15</td>
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<tr>
<td>48 h</td>
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<td>0-49</td>
<td>0-16, 1-46</td>
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<td>1-04</td>
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<td>Pancreatic infectious complications</td>
<td>0-44</td>
<td>0-23, 0-84</td>
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<td>0-73</td>
<td>0-33, 1-63</td>
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<td>0-60</td>
<td>-0-96</td>
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<td></td>
<td>Severe acute pancreatitis</td>
<td>Multiple organ failure</td>
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<td>0-27, 0-77</td>
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<td>0-31</td>
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<td>Mortality</td>
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<td>0-67</td>
<td>0-22, 2-10</td>
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<td>Pancreatic infectious complications</td>
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<td>0-22</td>
<td>0-01, 4-07</td>
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<td>Mortality</td>
<td>0-46</td>
<td>0-25, 0-87</td>
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<td>0-34</td>
<td>0-06, 1-85</td>
<td>0-21</td>
<td>1-35</td>
<td>0-62</td>
<td>0-43</td>
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</table>

RR, risk ratio of enteral nutrition vs. parenteral nutrition.

Fig. 3. Forest plot of risk ratios (RR) of pancreatic infectious complications in patients with both mild and severe acute pancreatitis who received enteral nutrition (EN) or parenteral nutrition (PN) within and after 48 h of admission.
nutrition, which varied in the literature from 24 h after the onset of symptoms to 72 h after admission. In particular, the ‘cut-off’ time points of 24 h and 48 h after admission were recommended by the ESPEN (European Society for Parenteral and Enteral Nutrition) and ASPEN (American Society for Parenteral and Enteral Nutrition) guidelines, respectively. In line with these recommendations, we arbitrarily considered the same time points. Second, eight of eleven RCT did not provide the data on timing between the onset of symptoms and admission, potentially confounding individuals at different points in the development of their disease. Third, several authors excluded patients who died early in the course of disease or needed a surgical intervention, thereby skewing the outcome data.

In conclusion, the present systematic review shows a significant risk reduction of multiple organ failure, pancreatic infectious complications and mortality with the use of enteral over parenteral nutrition in acute pancreatitis. Notably, these benefits of enteral nutrition are significant when the nutrition is administered within 48 h of admission, whereas the effectiveness of the two types of artificial nutrition does not differ significantly when the commencement of nutrition is delayed. The latter findings may warrant further investigation in an adequately powered randomised study on early vs. delayed enteral nutrition in patients with acute pancreatitis.

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M. S. P is the guarantor of the article.

M. S. P. conceived of the study. M. S. P. and R. D. P. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. M. S. P. and R. D. P. analysed the data. M. S. P. drafted the manuscript and all other authors critically revised it. All authors read and approved the final manuscript.

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