Acute and chronic pancreatitis: epidemiology and clinical aspects
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Nutritional management of patients with acute pancreatitis: a Dutch observational multicenter study

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on behalf of the other members of the EARL study group (see appendix)
Summary

**BACKGROUND** Following a nil per os regimen, most patients with acute pancreatitis can resume normal oral intake within one week. If not tolerated, it is recommended to initiate artificial feeding, preferably by the enteral route.

**AIM** To evaluate the nutritional management of patients with acute pancreatitis in a Dutch cohort (EARL study).

**METHODS** Observational study in 18 hospitals. Total days of nil per os, tube feeding with/without oral feeding, total parenteral nutrition, and total starvation time were analyzed.

**RESULTS** In mild acute pancreatitis, the majority of cases with a nutritional intervention (117/145, 80.7%; 95% CI: 73.5-86.3) were managed with a nil per os regimen only. Twenty-seven patients (18.6%; 95% CI: 13.1-25.7) with mild acute pancreatitis additionally received tube feeding. Of those with severe acute pancreatitis more than half of the patients (9/16, 56.3%; 95% CI: 33.2-76.9%) were treated with tube feeding besides a nil per os regimen. Tube feeding was delivered preferably via the jejunal route. The median period of total starvation was two days for both mild and severe acute pancreatitis. Only 5.5% (9/164; 95% CI: 2.9-10.1) of all patients had a prolonged starvation time of more than 5 days.

**CONCLUSIONS** The total time of starvation was limited in the majority of patients admitted for acute pancreatitis. According to international guidelines, additional nutritional interventions were quickly undertaken with enteral feeding via the jejunum as the preferred route.
Introduction

The clinical course of acute pancreatitis (AP) is mild in most cases and treatment is mainly supportive.1-5 Besides adequate pain management a nil per os (NPO) regimen often started.5,7 The rationale for a period without food intake is based on the assumption that pancreatic stimulation by oral feeding may deteriorate pancreatic inflammation.7,9 Moreover, many patients are anorectic because of feelings of nausea and suffer from increased pain sensations when eating. The resumption of oral feeding depends on improvement of abdominal pain, absence of nausea, and return of appetite. If these conditions are met, patients are typically put on a clear liquid diet first and, if tolerated well, the diet is expanded to full liquids or low-fat solids. One recent randomized trial showed that the resumption of a low fat solid diet after a mild AP attack appeared to be safe and provided more calories than a clear liquid diet.10 Even immediate resumption of oral feeding was feasible and safe in a small randomized trial.11 Several practice guidelines for mild AP recommend to initiate enteral nutrition, if patients cannot consume normal food after 5-7 days.6, 7, 12-15 For severe AP nutritional support is indicated when it becomes evident that the patient will not be able to tolerate oral intake for a prolonged period of time, e.g. for at least 7 days. This assessment can usually be made within the first 3-4 days of admission.6 Tube feeding (TF) is preferred over total parenteral nutrition (TPN). TF reduces significantly the infection rate of necrosis and lowers the need for surgery in patients with severe AP.4 TPN should only be used in patients unable to tolerate enteral nutrition. Although not investigated for AP, it seems likely that (severe) undernutrition affects disease outcome negatively.14 Consequently, it is plausible, that the total starvation time during hospitalization should be kept as short as possible (e.g. five days or less). We evaluated the nutritional management and the total starvation time in a Dutch cohort of patients with AP or with recurrent AP.

Methods

Study population

In August of 2003 an observational prospective multicenter cohort study in the province of Northern Holland was initiated (the EARL study). The period of inclusion of patients ended in May 2006. Patients with AP or recurrent AP were included from 18 hospitals (2 academic hospitals and 16 general teaching hospitals). The study protocol was approved by all local ethics committees and informed consent was obtained from patients before inclusion. AP was defined as a clinical picture with acute epigastric pain combined with a serum amylase and/or lipase value of more than three times the upper limit of normal, and with the absence of any feature of CP. Disease severity (mild and severe AP) was defined according to the Atlanta criteria.16 Recurrent AP was defined as more than one
nutritional management of acute pancreatitis

attack of AP in the time before inclusion and/or during the observation period. From the study database, we retrieved all patients with a confirmed diagnosis of AP or recurrent AP together with at least one completed review of a hospital admission. As nutritional management in subsequent admissions for recurrent AP may be affected by earlier admissions, only the first documented hospital admission was included in the analysis.

Hospital records and nursing reports were thoroughly reviewed and study items were recorded in a dedicated database. The following data were retrieved from this study database: demographic data, etiological factors, hospitalization time, department of admission, presence of local complications (pseudocyst, abscess, pancreatic necrosis) and total days of NPO, TF with/without oral feeding, route of TF (gastric versus jejunal) and use of TPN. The tolerance of the nutritional management (e.g. relapse of pain, nausea, vomiting) and the different formulas of artificial nutrition prescribed and used by patients with tube feeding were not recorded.

NPO was defined as a nil per os regimen with or without drinking water (no calories, proteins or fat are involved). As soon as the liquids contained any amount of calories, this was defined as oral feeding. The total starvation time was defined as the number of days in which the patient did not received any enteral or parenteral feeding (calories).

The aetiology was assessed after a thorough review of hospital and out-patient charts regarding reported alcohol consumption and drug use (retrieved from hospital charts and study questionnaires), laboratory results (e.g. liver function tests, triglycerides, calcium) and imaging procedures (e.g. ultrasound, CT, MRCP, ERCP and EUS).

CT scans of patients with severe AP were reviewed by an expert radiologist from a tertiary referral hospital. This re-evaluation was performed in order to prevent misclassification of local complications, e.g. especially the development of pancreatic or peri-pancreatic necrosis.

The radiologist re-evaluated (blinded for the results of the original report) the presence of local complications according to the Atlanta criteria.

Statistics

In this observational study descriptive statistics were used. The analysis was performed for mild and severe AP admissions separately. Categorical data were reported as proportions along with Wilson’s 95% confidence intervals (95% CI) and quantitative data as medians with ranges. For non-normally distributed data the Mann-Whitney U test was used for group comparisons. To evaluate the associations between the severity of the course of AP on the one hand and type of nutritional intervention on the other, the Pearson’s Chi square test was used. To minimize low cell frequencies, data were meaningfully dichotomized. In case of remaining low cell frequencies below 5, either the Yates’s correction for continuity was applied (for n=3 or n=4) or Fisher’s exact test was performed (n≤2). Statistical significance was defined as a P value less than .05. All statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 12.0.1 (SPSS, Chicago, IL).
Results

Aetiology, disease course and hospital stay

From the study database 198 hospital admissions regarding 164 patients with AP or recurrent AP were retrieved. Twenty patients had more than one documented hospital admission during the study period. Only the first documented admission was included in the present analysis.

The baseline characteristics of the study population are presented in Table 1. The proportion of male and female patients was the same and the median age at the first reviewed hospital admission was 50 years (range 18-95). Almost one quarter of patients suffered from recurrent attacks of AP. The most common etiological factor was a biliary cause (69/164, 42.1%; 95% CI: 34.8-49.7) followed by an unknown cause. Importantly, this latter group consisted of patients with an idiopathic pancreatitis (19/164, 11.6%; 95% CI: 7.5-17.4), but also of patients with an (as yet) unknown cause because the di-

Table 1  General characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>N=164</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>82 (50)</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>50 (18-95)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td></td>
</tr>
<tr>
<td>• First attack (%)</td>
<td>124 (75.6)</td>
</tr>
<tr>
<td>• Recurrent attacks (%)</td>
<td>40 (24.4)</td>
</tr>
<tr>
<td>Aetiology (%)</td>
<td></td>
</tr>
<tr>
<td>• Biliary</td>
<td>69 (42.1)</td>
</tr>
<tr>
<td>• Unknown*</td>
<td>33 (20.1)</td>
</tr>
<tr>
<td>• Alcohol</td>
<td>31 (18.9)</td>
</tr>
<tr>
<td>• Post ERCP</td>
<td>19 (11.6)</td>
</tr>
<tr>
<td>• Drugs</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>• Tumor/obstruction</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>• Pancreas divisum</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>• Hypertriglyceridemia</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Course of acute pancreatitis</td>
<td></td>
</tr>
<tr>
<td>• Mild</td>
<td>148 (90.2)</td>
</tr>
<tr>
<td>• Severe</td>
<td>16 (9.8)</td>
</tr>
<tr>
<td>• Organ failure</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>• Necrosis†</td>
<td>10 (62.4)</td>
</tr>
<tr>
<td>• Abscess</td>
<td>4 (25)</td>
</tr>
<tr>
<td>• Pseudocyst</td>
<td>1 (6.3)</td>
</tr>
</tbody>
</table>

* Combination of 19 patients with idiopathic pancreatitis and 14 patients with an unknown cause whereby the diagnostic work up for an etiological factor has not fully been completed
† Pancreatic necrosis and/or peripancreatic necrosis
agnostic work up for an etiological factor was not fully completed (14/164, 8.5%; 95% CI: 5.2-13.8). Alcoholic AP was the third most common cause (31/164, 18.9%; 95% CI: 13.6-25.6). In 90.2% (148/164, 95% CI: 84.7-93.9) of cases the disease course was mild. The development of pancreatic necrosis was the most common local complication during the admissions of a severe AP [table 1]. Table 1 lists the local complications established after re-evaluation of the CT scans by the expert radiologist. Ten out of 16 patients with severe AP developed pancreatic necrosis and/or peripancreatic necrosis.

The majority of cases, both mild and severe, were admitted to a general teaching hospital, 68.2% (101/148, 95% CI: 60.4-75.2) and 56.3% (9/16, 95% CI: 33.2-76.9), respectively. More than 90% (134/148, 95% CI: 84.7-94.3) of the mild AP were admitted to an internal medicine/gastroenterology ward, whereas half of the severe AP patients were clinically managed by surgeons.

**Nutritional management**

During almost all hospital admissions some form of nutritional intervention was carried out [table 2]. In the majority of cases with mild AP a NPO regimen was followed as the sole nutritional intervention (117/145, 80.7%; 95% CI: 73.5-86.3). The median duration of NPO was 2 days (range 1-12). In 17.2% (25/145, 95% CI: 12-24.2) of mild AP admissions a NPO regimen was combined with a period of TF (sole or combined with oral feeding) via the jejunal route. The median duration of TF via the jejunal route was 10 days (range 1-28). All jejunal feeding tubes were placed by endoscopy. Two mild AP patients received TF via the gastric route (5 and 6 days) and one patient received supplementary TPN for 11 days.

**Table 2**  **Overall nutritional management during hospital admissions for mild and severe acute pancreatitis**

<table>
<thead>
<tr>
<th>Nutritional intervention</th>
<th>Mild AP (N=148)</th>
<th>Severe AP (N=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No nutritional intervention(s) (%)</td>
<td>3 (2)</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>Nutritional intervention(s) (%)</td>
<td>145 (98)</td>
<td>16 (100)</td>
<td>ns</td>
</tr>
<tr>
<td>Type of nutritional intervention</td>
<td>&lt;0.001‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• NPO only (%)</td>
<td>117 (80.7)</td>
<td>3 (18.8)</td>
<td></td>
</tr>
<tr>
<td>• NPO and TF-jejunal* (%)</td>
<td>25 (17.2)</td>
<td>9 (56.3)</td>
<td></td>
</tr>
<tr>
<td>• NPO and TF-gastric* (%)</td>
<td>2 (1.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>• TPN† (%)</td>
<td>1 (0.7)</td>
<td>4 (25)</td>
<td></td>
</tr>
<tr>
<td>• Median total starvation days (range)</td>
<td>2 (0-12)</td>
<td>2 (1-10)</td>
<td>ns</td>
</tr>
<tr>
<td>Median % starvation time of total admission days (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• All admissions</td>
<td>25 (0-100)</td>
<td>7.9 (1.5-57.1)</td>
<td>-</td>
</tr>
<tr>
<td>• Admission &gt;7 days</td>
<td>17.9 (0-70)</td>
<td>7.1 (1.5-26.7)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: NPO: nil per os, TF: tube feeding, TPN: total parenteral nutrition; ns: not significant; -: not tested
* TF sole or combined with oral feeding; † combined with NPO and TF via the jejunal route
‡ Calculated after dichotomizing for NPO only versus other types with or without NPO
Overall, artificial feeding was used in 18.9% (28/148, 95% CI: 13.4-26) of mild AP admissions.

In admissions for severe AP three (18.8%; 95% CI: 6.6-43) patients followed a NPO regimen as the sole nutritional intervention for 2, 4 and 4 days, respectively. More than half (9/16, 56.3%; 95% CI: 33.2-76.9) of the patients followed a NPO regimen combined with a period of TF via the jejunal route. The median duration of TF was 31 days (range 12-47). Four patients (25%; 95% CI: 10.2-49.5) with severe AP received supplementary TPN for 5, 7, 9 and 12 days, respectively. Overall, nutritional support by some form of artificial feeding was installed in 81.3% (13/16, 95% CI: 57-93.4) of severe AP admissions.

The observed nutritional management in mild AP admissions resulted in a median total starvation time of 2 days (range 0-12). One female patient was kept for 12 days on a NPO only regimen. She was admitted during 21 days for a mild post ERCP pancreatitis, resulting in a total starvation time of 57.1% (12/21, 95% CI: 36.5-75.5) of the total days of admission. In severe AP admissions the median total starvation time was also 2 days (range 1-10). The median percentage time of starvation was 25% (range 0-100) and 7.9% (1.5-57.1) of the total hospitalization time for mild and severe AP, respectively. When only the admissions of >7 days were taken into account, these percentages decrease to 17.9% (range 0-70) and 7.1% (range1.5-26.7), respectively. Due to the equivalence in starvation time for mild and severe AP these results (not tested for redundancy) coincide with the reported difference in hospital stay. In this latter subgroup, the starvation time was more than 5 days in 7.8% (7/90, 95% CI: 3.8-15.2) and 13.3% (2/15, 95% CI: 3.7-37.9) for mild and severe AP admissions. Notably, no patients had a starvation time of more than 5 days when admitted less than one week. Overall, 5.5% (9/164, 95% CI: 2.9-10.1) of all patients during admission had a prolonged starvation time of more than 5 days.

Discussion

The present report is an observational study in which the overall nutritional management by attending physician(s) at the time of admission for AP was assessed in a Dutch multi-center setting. In this series, the overall nutritional management resulted in a limited total starvation time for the majority of the patients. In mild AP, most patients (80.7%) were managed by a NPO regimen only for a short period of time, whereas in severe AP a NPO regimen combined with TF was the preferred choice of treatment (56.2%). Any form artificial feeding was initiated in 18.6% of mild AP and in 81.3% of severe AP admissions. At first glance this seems in accordance with a recent Italian multicentre survey in which nutritional support was used in 26.7% and 80.2% for mild and severe AP, respectively. However, striking differences were found with regard to the choice and type of artificial feeding. In the Italian study enteral nutrition was much underutilized and TPN, sole or in combination with enteral nutrition, was administered to 95.3% of
mild and severe AP patients. On the contrary, a recent survey in Germany concluded that three out of four gastroenterologists preferred enteral parenteral nutrition, but this study did not show whether this preference was put into practice. The impact of the different etiological factors on the subsequent nutritional management has not been analyzed, because of the range of different aetiologies and the inherent small group per aetiology. Furthermore, nutritional management in AP is more often led by disease severity and to a lesser extend by the different aetiologies.

In the present series the timing, type and frequency of the observed interventions with regard to nutritional management seem to be well in line with several practice guidelines for AP. Notably, Dutch physicians are well informed about the guidelines for the nutritional management in AP. In part, this is most probably the resultant of frequent exchanges of information during well attended consensus meetings on various subjects including pancreatitis by gastroenterologists and surgeons in a relatively small country. Second, an awareness campaign concerning the prevention of undernutrition in hospitalized patients that was initiated by Dutch physicians and health authorities in 2000 may have led to an earlier initiation of feeding.

In mild AP it is recommend to start with enteral nutrition if patients cannot consume normal food within 5-7 days. For severe AP, nutritional support is indicated when it becomes clear that the patient will not be able to tolerate oral intake for a prolonged period of time. According to the Practice Guidelines in AP of the American College of Gastroenterology, this assessment can usually be made within 3-4 days after hospital admission, after which nutritional support should be instituted. TF is preferred over total parenteral nutrition. In this series only in a minority of patients TPN was used and almost exclusively during admission for severe AP. Only one patient with a mild AP was treated with supplementary TPN for several days.

In clinical practice, patients with AP are first kept on a NPO regimen. The resumption of oral feeding depends on the improvement of abdominal pain, absence of nausea, and on the return of appetite. Typically, patients are put on a clear liquid diet and, if well tolerated, the diet is gradually expanded to normal food. The resumption of oral feeding may be temporarily halted because of a relapse or deterioration of abdominal pain and/or nausea. A recent review showed that in 17.2% of cases the pain relapsed after resumption (within 48 hours) of oral feeding. The relapse of pain may be an important factor that negatively influences the duration of the total starvation time. Notably, in this study is the severity of AP was classified according to the Atlanta criteria. However, also patients with a ‘mild’ AP according to the Atlanta criteria may run a clinically ‘severe’ course due to prolonged pain complaints and/or ileus without the presence of pancreatic necrosis.

In our study, TF was delivered in most cases via the jejunal route. In only two patients with mild AP, TF was delivered via the nasogastric route. In 2000, Eatock et al. were the first to publish a study about the possibility of using early nasogastric feeding
in severe AP, which appeared to be safe and well-tolerated. Since, 3 randomized controlled trials have been published regarding early nasogastric feeding in severe AP and a meta-analysis including 131 patients showed no significant differences in mortality rates between nasogastric and conventional routes of feeding. Additional outcome parameters such as length of hospital stay, infectious complications, multiple organ deficiency syndrome, rates of admissions to the ICU or conversion to surgery were also not significantly different. The recurrences of pain on refeeding and adverse events associated with nutrition were similar between groups. Given the positive outcome of this meta-analysis and the ease by which a nasogastric feeding tube can be placed, this might well become the preferred route by which TF is administered.

Importantly, in this Dutch multi-center observational study we document that nutritional management resulted in a limited total starvation time for the vast majority of the patients. A relatively small percentage of patients (5.5%) experienced a prolonged starvation time of more than 5 days. Most of these patients had mild AP. Whether these patients or patients who did receive additional nutritional measures suffered from undernutrition was not a subject of this study. However, it does not seem unlikely that some patients may have suffered some extent of undernutrition as interventional nutritional measures were initiated after a certain period of starvation and did not always result instantly in a daily delivery of an amount of calories required on the basis of patients’ bodyweight and severity of illness. Although the association between (severe) undernutrition and the outcome of AP has not been properly investigated, it has been shown that undernutrition is associated with a worse disease outcome and higher morbidity. Marik et al. showed in a meta-analysis of 15 randomized trials with critically ill patients (other than AP) that enteral nutrition within 24 hours after admission was associated with a lower incidence of infectious complications compared with delayed enteral nutrition.

In conclusion, in this cohort of Dutch patients admitted because of an attack of acute (recurrent) pancreatitis, the total time of starvation was limited for the majority of patients. According to international guidelines, additional nutritional interventions were undertaken early in the course of the disease with enteral feeding via the jejunum as the preferred route. A small minority of patients suffered from prolonged starvation which may potentially hamper recovery and outcome. Therefore, physicians should remain vigilant with regard to the nutritional status and nutritional requirements of patients admitted for AP. Further studies are needed to investigate the possible presence of (severe) undernutrition in both mild and severe AP and whether undernutrition negatively affects the outcome of AP.
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Appendix

Other members of the EARL study group:

A.A. van Bodegraven, VU University Medical Center, Amsterdam, Amsterdam; I.C.E. Wesdorp, Sint Lucas/Andreas Hospital, Amsterdam; H.A. van Heukelem, Slotervaart Hospital, Amsterdam; A.A. Geraerdts, Onze Lieve Vrouwe Gasthuis, Amsterdam; A. Teunen, Boven IJ Hospital, Amsterdam; L.A. Noach, Amsteland Hospital, Amstelveen; W. Bruins Slot, Spaarne Hospital, Hoofddorp; G.H. de Groot, Red Cross Hospital, Beverwijk; R.J.L.F. Loffeld, Zaans Medical Center, Zaanstad; P.P. Viergever, Gemini Hospital, Den Helder; M. Klemt, Westfries Gasthuis, Hoorn; P.R. Oosting, Waterland Hospital, Purmerend; M.J. Wagtmans, Flevo Hospital, Almere; P.J. Kingma, Tergooiziekenhuizen, location Blaricum; C.Y. Ponsioen, Tergooiziekenhuizen, location Hilversum
References
